SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc
Device Trade Name:	PCM® Cervical Disc
Device Procode:	MJO
Applicant's Name and Address:	NuVasive®, Inc. 7475 Lusk Blvd. San Diego, CA 92121
Date of Panel Recommendation:	none
Premarket Approval Application (PMA) Number:	P100012
Date of FDA Notice of Approval:	October 26, 2012
Expedited:	not applicable

II. INDICATIONS FOR USE

The PCM Cervical Disc is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and manifested by at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. The PCM Cervical Disc is implanted using an anterior approach. Patients should have failed at least 6 weeks of conservative treatment prior to implantation of the PCM Cervical Disc.

III. CONTRAINDICATIONS

The PCM Cervical Disc should not be implanted in patients with the following conditions:

- Acute or chronic infections, local or systemic
- Osteoporosis (defined as DEXA bone density measured T-Score $\leq$ -2.5) or osteopenia (defined as DEXA bone density measured T-Score $\leq$ -1.0)
- Congenital stenosis
- Allergy or sensitivity to *any* of the implant materials (cobalt, chromium, molybdenum, titanium, or polyethylene)

IV. WARNINGS AND PRECAUTIONS

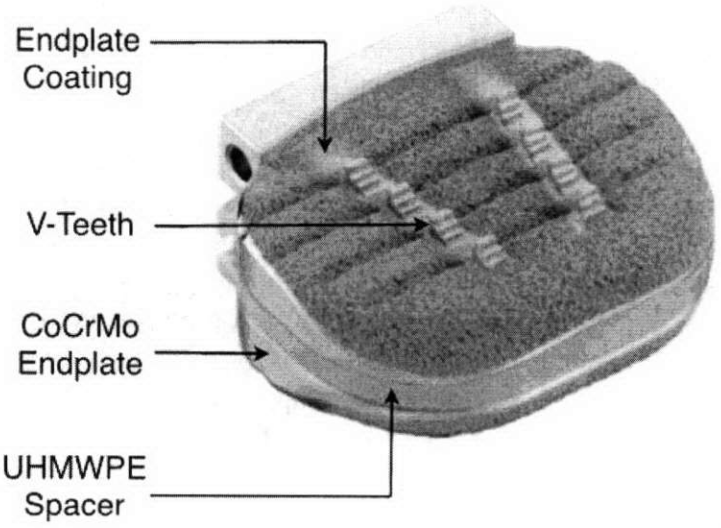
The warnings and precautions can be found in the PCM Cervical Disc physician labeling.

V. DEVICE DESCRIPTION

The PCM Cervical Disc is a two-piece articulating device that is inserted into the intervertebral disc space at a single cervical level using a standard anterior cervical approach, known as the Smith-Robinson anterior approach.

The PCM Cervical Disc is comprised of two cobalt chromium molybdenum (CoCrMo) alloy metal endplates, one cephalad and one caudal, and an ultra-high molecular weight polyethylene (UHMWPE) spacer fixed to the caudal endplate. The articulation consists of a superior concave metallic surface and the inferior polyethylene convex surface. The plates are available in three sizes (small, medium, and large). The dimensions of the endplates are 14 × 17 mm (small), 16 × 17 mm (medium), and 17 × 20 mm (large). The PCM Cervical Disc comes in overall thicknesses of 6.5, 7.2, and 8.0 mm. The contact between the UHMWPE spacer and the cephalad component is ball-and-socket articulation. Refer to ***Table 1*** for a complete listing of part numbers. The bone-contacting surface of each of the endplates has a coating that is comprised of two layers of titanium covered by an electrochemically applied layer of calcium phosphate (TiCaP®). This surface has transverse ridges designed to enhance postoperative bone fixation.

Figure 1: PCM Cervical Disc (PCM-V)



The PCM Cervical Disc implant materials consist of the following:

- CoCrMo Alloy, according to ISO 5832-12
- UHMWPE, according to ISO 5834-1, ISO 5834-2 / ASTM F648
- Unalloyed Titanium, according to ISO 5832-2 / ASTM F67
- Titanium plasma spray (TPS) and calcium phosphate (CaP) coatings

Table 1: PCM Cervical Disc Configurations

Part Number	Description
7680265	PCM-V Disc, S 6.5
7680272	PCM-V Disc, S 7.2
7680280	PCM-V Disc, S 8.0
7680365	PCM-V Disc, M 6.5
7680372	PCM-V Disc, M 7.2
7680380	PCM-V Disc, M 8.0
7680465	PCM-V Disc, L 6.5
7680472	PCM-V Disc, L 7.2
7680480	PCM-V Disc, L 8.0

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-operative alternative treatments for intractable radiculopathy or myelopathy due to a single-level abnormality localized to the disc space include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.

In addition, there are alternative surgical techniques which include, but are not limited to, surgical decompression, with or without fusion using various bone grafting techniques (e.g., Cloward bone dowels, Smith Robinson tri-cortical wedges, and keystone grafts) sometimes used in conjunction with anterior spinal systems (e.g., plate and screw systems), posterior spinal systems (e.g., screw/rod, plate systems, posterior wiring systems), cage devices, or other approved cervical discs. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The PCM Cervical Disc has been available in markets outside of the United States since 2002. The device has not been withdrawn from the market for any reason relating to the safety and effectiveness of the devices. The countries in which the PCM Cervical Disc is available are as follows: Argentina, Australia, Belgium, Brazil, Canada, China, Finland, Germany, Greece, Italy, Lithuania, Mexico, Netherlands, New Zealand, Norway, Peru, Portugal, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, and the United Kingdom. The device has not been withdrawn from the market for any reason relating to the safety and effectiveness of the devices.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential risks associated with the use of the PCM Cervical Disc include: 1) those commonly associated with any surgery; 2) those specifically associated with cervical spinal surgery using an anterior approach; and 3) those associated with a spinal implant, as well as those pertaining to the PCM Cervical Disc. However, the causality of these adverse events is not exclusive to these categories. There is also the risk that this surgical procedure will not be effective, and may not relieve or may cause worsening of preoperative symptoms. Some of these effects were observed in the clinical study and are therefore reported in Section X, Summary of Clinical Studies below.

- Risks associated with any surgical procedure are those such as: abscess; cellulitis; wound dehiscence; wound necrosis; edema; hematoma; heart and vascular complications; hypertension; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; pulmonary complications; organ, nerve or muscular damage; gastrointestinal compromise; seizure, convulsion, or changes to mental status; and complications of pregnancy including miscarriage and fetal birth defects;
- Risks associated with anterior intervertebral body surgery of the cervical spine include: dysphagia; dysphasia; dysphonia; hoarseness; vocal cord paralysis; laryngeal palsy; sore throat; recurring aspirations; nerve deficits or damage; tracheal, esophageal, or pharyngeal perforation; airway obstruction; external chylorrhea; warmth or tingling in the extremities; damage to the spinal cord, nerve roots, or nerves possibly resulting in paralysis or pain; dural tears or leaking; cerebrospinal fistula; discitis, arachnoiditis, and/or other types of inflammation; loss of disc height; loss of proper curvature, correction, height or reduction of the spine; vertebral slipping; scarring, herniation or degeneration of adjacent discs; surrounding soft tissue damage, spinal stenosis; spondylolysis; otitis media; fistula; vascular damage and/or rupture; seromas or tissue swelling; and headache;
- Risks associated with implants in the spine, including the PCM Cervical Disc device, are: early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; malposition of the implant; loss of purchase; sizing issues with components; anatomical or technical difficulties; implant fracture; bone fracture; skin penetration; irritation, pain, bursitis resulting from pressure on the skin from component parts in patients with inadequate tissue coverage; foreign body reaction to the implants, including possible tumor formation, autoimmune disease, metallosis, and/or scarring; possible tissue reaction; bone resorption; bone formation that may reduce spinal motion or result in a fusion, either at the treated level or at adjacent levels; development of new radiculopathy, myelopathy or pain; tissue or nerve damage caused by improper positioning and placement of implants or instruments; loss of neurological function; decreased strength of extremities; decreased reflexes; cord or nerve root injury; loss of bowel and/or bladder control; and interference with radiographic imaging because of the presence of the implant;
- Wound, local and/or systemic infections;
- Surgical instrument bending or breakage, as well as the possibility of a fragment of a broken instrument remaining in the patient;
- Inability to resume activities of normal daily living; and
- Death.

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IX. SUMMARY OF PRECLINICAL STUDIES

A. Biomechanical Tests

A series of mechanical tests and animal studies were performed to characterize the properties and function of the PCM Cervical Disc.

The IDE study included two different configurations of the PCM Cervical Disc referred to as PCM-Standard and PCM-V, featuring identical sizes, general design configurations, materials, coatings, and articulation. The sponsor introduced the PCM-V to provide another means of immediate fixation of the device to help prevent initial migration of the implant. The only differences in design between the PCM-Standard and PCM-V are as follows:

- The PCM-V has two rows of small "teeth" (1 mm in height) on the bone-contacting surface of each of the endplates that are angled toward each other in a "V" configuration.
- A reduction in the number of ridges along the endplate surface was made to the PCM-V in order to allow space to include the teeth.

It should be noted that The PCM-V was allowed to be incorporated into the study based on pullout testing (see Table 2 below) and future sub-group analyses (see Clinical Section below). The sub-group analyses showed that the two device cohorts were poolable. In PMA P100012, the applicant is only seeking marketing approval for the PCM-V.

The PCM-Standard device is representative of the PCM-V for all the biomechanical testing except where both devices were tested.

Table 2: Summary of Preclinical Biomechanical and Animal Testing

BIOMECHANICAL TESTING

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Axial Compression	To evaluate the static axial compression performance of the PCM device, under worst case conditions.	Five (5) PCM-Standard specimens were tested under static compression in 37°C saline at a rate of 25 mm/min until failure or 2 mm displacement.	Yield load must be greater than the maximum compressive load a cervical vertebral segment can withstand (1.75 kN).[1]	The average load at 2 mm displacement was 18.7 ± 2.03 kN. These results suggest that the PCM device can withstand axial compression loading that exceeds the anticipated physiologic loads on the cervical spine.
Dynamic Axial Compression	To evaluate the dynamic axial compression performance of the PCM device, under worst case conditions.	Seven (7) PCM-Standard specimens were tested under dynamic axial compression in 37°C saline to 10 million cycles, using a sinusoidal wave form with R=10 at 1 Hz.	Fatigue load must be greater than the maximum compressive load on a cervical intervertebral disc (155 N).[2]	Two specimens ran out to 10 million cycles under an 800 N load. These results suggest that the PCM device can withstand dynamic axial compression loading that exceeds the anticipated physiologic loads on the cervical spine.
Static Compression-Shear	To evaluate the static compression-shear performance	Five (5) PCM-Standard specimens were	Yield load must be greater than the maximum shear load that	The average 2% offset yield load was 1052 ± 72 N, with an average displacement of 1.51 ± 0.18 mm.

	of the PCM device, under worst case conditions.	tested under static compression in 37°C saline at a rate of 25 mm/min until failure or 2 mm displacement.	a cervical intervertebral disc can receive in a posterior impact situation (270 N).[3]	These results suggest that the PCM device can withstand compressive loading that exceeds the anticipated physiologic loads on the cervical spine.
Dynamic Compression-Shear	To evaluate the dynamic compression-shear performance of the PCM device, under worst case conditions.	Seven (7) PCM-Standard specimens were tested under dynamic axial compression in 37°C saline to 10 million cycles, using a sinusoidal wave form with R=10 at 1-1.35 Hz.	Fatigue load must be greater than the maximum shear load that a cervical intervertebral disc can withstand (39 N).[4]	Two specimens ran out to 10 million cycles under a 350 N load. These results suggest that the PCM device can withstand dynamic compression-shear loading that exceeds the anticipated physiologic loads on the cervical spine.
Device Pullout	To evaluate and compare the device pullout performance of the PCM Standard and PCM-V devices, under worst case conditions.	Eight (8) PCM-Standard and 8 PCM-V specimens were tested for device pullout in ambient air at a rate of 2.5 mm/min.	Maximum load must be greater than the maximum pullout load for of a tri-cortical iliac crest graft (162 N).[5]	The average maximum load was 257.4 ± 28.5 N for the PCM Standard and 308.1 ± 15.3 N for the PCM-V. These results suggest that the PCM device can withstand device pullout loading that exceeds the anticipated physiologic loads on the cervical spine.
Core Expulsion	To evaluate the core expulsion performance of the PCM device, under worst case conditions.	Five (5) PCM-V specimens were tested for core expulsion in ambient air at a rate of 6 mm/min.	Maximum load must be greater than the maximum shear load that a cervical intervertebral disc can withstand (39 N).[6]	The average maximum load was 855.6 ± 40.5 N, with an average displacement of 1.75 ± 0.14 mm. These results suggest that the PCM device can withstand core expulsion loading that exceeds the anticipated physiologic loads on the cervical spine.
Subluxation	To evaluate the subluxation performance of the PCM device, under worst case conditions.	Five (5) PCM-V specimens were tested for subluxation in ambient air at a rate of 6 mm/min.	Maximum load must be greater than the maximum shear load that a cervical intervertebral disc can withstand (39 N).[7]	The average maximum load was 83.2 ± 7.6 N, with an average displacement of 2.19 ± 0.73 mm. These results suggest that the PCM device can withstand subluxation loading that exceeds the anticipated physiologic loads on the cervical spine.
Subsidence	To evaluate the subsidence performance of the PCM device, under worst case conditions.	Five (5) PCM-V specimens were tested for subsidence in ambient air at a rate of 6 mm/min.	Yield load must be greater than the maximum compressive load on a cervical intervertebral disc (155 N).[8]	The average yield load was 1187.3 ± 13.7 N, with an average displacement of 3.51 ± 0.12 mm. These results suggest that the PCM device can withstand subsidence loading that exceeds the anticipated physiologic loads on the cervical spine.
Durability/ Wear Testing	To characterize the wear performance of the small footprint PCM device under Draft ASTM F2423-05 motion.	Five (5) PCM specimens were tested under Draft ASTM F2423-05 conditions (±10° fully reversing lateral bending, ±6° fully reversing axial	This testing was performed to establish the wear characteristics of the small footprint PCM device under Draft ASTM F2423-05 parameters. Implant failure should not occur as a result of the testing.	Average cumulative wear at 10 million cycles was 71.22 ± 17.56 mg. The wear rate was 0.042 mg/million cycles between 3 Mc and 10 Mc. Average wear debris particle sizes determined by low-angle laser light scattering (LALLS) was 2.16 ± 1.19 μm (number basis). No implant failure was observed.

		rotation, 100 N axial load) to 10 million cycles (Mc) at 1-1.35 Hz.		This initial wear testing showed experimental inconsistencies due to (i) fixture degradation, with apparent high wear during the first 3 Mc, and (ii) larger wear particle sizes than expected. See additional wear testing below.
Durability/ Wear Testing	To characterize the wear performance of the small footprint PCM device under worst-case 3-axis cross-shear ISO 18192-1 motion.	Six (6) PCM specimens were tested under ISO 18192-1 cervical conditions to 10 Mc at 1 Hz.	This testing was performed to establish the wear characteristics of the small footprint PCM device under ISO 18192-1 parameters. Implant failure should not occur as a result of the testing.	Average cumulative wear at 10 million cycles was 64.06 ± 2.55 mg and the wear rate was 6.33 mg/million cycles between 1 and 10 Mc. Average central height loss of the inferior component at 10 million cycles was 0.45 ± 0.01 mm. Average wear debris particle sizes determined by SEM were 0.53 ± 0.15 µm and 0.43 ± 0.04 µm, and average aspect ratios were 1.96 ± 0.11 and 2.03 ± 0.12 for the 2 specimens. Particles were smooth globular with some twisted fibrillar at all magnification ranges. No implant failure was observed.
Durability/ Wear Testing	To characterize the wear performance of the large footprint PCM device under worst-case 3-axis cross-shear ISO 18192-1 motion.	Six (6) PCM specimens were tested under ISO 18192-1 cervical conditions to 10 Mc at 1 Hz.	This testing was performed to establish the wear characteristics of the large footprint PCM device under ISO 18192-1 parameters. Implant failure should not occur as a result of the testing.	One test device was noted to wear through the polyethylene core to the titanium alloy locking plate at 5 Mc. As a result, the test was terminated at 5 Mc. Average cumulative wear at 5 Mc was 38.2 ± 0.70 mg and the wear rate was 7.37 mg/million cycles between 1 and 5 million cycles. Average central height loss of the inferior component at 5 Mc was 0.19 ± 0.03 mm. Information was presented to support that these test conditions may not be representative of those under which the device would operate *in vivo*.
Durability/ Wear Testing	To characterize the wear performance of the large footprint PCM device using modified ISO 18192-1 motion parameters derived from clinical measurements from the IDE study.	Six (6) PCM specimens were tested under ISO 18192-1 cervical conditions to 5 Mc at 1 Hz.	Wear testing was performed to establish the wear characteristics of the large footprint PCM device under ISO 18192-1 with modified motion parameters derived from IDE study data. Implant failure should not occur as a result of the testing.	Average cumulative wear at 5 Mc was 16.0 ± 0.87 mg. The steady-state wear rate was 2.86 mg/million cycles between 2 and 5 million cycles. Average central height loss of the inferior component at 5 Mc was 0.096 ± 0.008 mm. No implant failure was observed.

PRECLINICAL ANIMAL TESTING

The PCM device was implanted into the cervical spine of goats to evaluate the short-term biological and mechanical responses t the device *in vivo*. There was no evidence of mechanical loosening and there were no adverse reactions to the device. Particulate wear debris animal testing was performed to characterize the biological response to the device. Rabbits were implanted with acute doses of CoCr particles and UHMWPE particles directly on the dura. There was no evidence of acute histopathological response to the materials.

Test Name	Purpose	Method	Acceptance Criteria	Results
Caprine Study	To characterize the biological and biomechanical response to the device.	Goats were implanted with the PCM device at C3-C4. Six and 12 month time-points were evaluated for histology, immuno-cytochemistry, and range of motion.	Animal implantation testing was performed to further establish the biological response to the device. An adverse biological response should not be present.	No animals displayed evidence of implant loosening or inflammatory reactions from particulate wear debris. Histologic evidence of osseous integration at the implant-bone interface was observed, and segmental motion was preserved between 6 and 12 months. These results suggest that the PCM device does not elicit an adverse biological response or restrict motion with time.
Wear Debris Particulate Animal Test	To characterize the biological response to wear debris from the device.	Rabbits were implanted with acute doses of CoCr particles or UHMWPE particles placed directly on the dura. Animals were sacrificed at 3 and 6 months.	Wear debris particulate animal testing was performed to establish the biological response to the device. An adverse biological response should not be present.	At both post-operative time periods, there was no evidence of an acute neural or systemic histopathological response to the materials included in this study. These results suggest that the PCM device does not elicit an adverse biological response.

Additional Discussion of Wear Testing

Four wear tests were completed as described in ***Table 2***. Results from the initial 10 million cycle (Mc) test per ASTM F2423-05 were inconsistent. This test was repeated to 10 MC under cross-shear (ISO 18192-1) motions using the same small footprint (14 × 17 mm), shortest height (6.5 mm) device size in order to clarify the initial results. On completion of the test, a new worst case device size for wear testing was established and an additional ISO test was performed on the large footprint device size (17 × 20 mm) with smallest thickness (6.5 mm) which was continued to 5 MC. The recommended range of motion (ROM) and subsequent cross-shear created under ISO 18192-1 may not be consistent with the *in vivo* kinematics of a large bearing radius, semi-constrained TDR device, such as PCM, for both the small and large footprint devices.

In order to develop a more clinically relevant wear test, ISO motion parameters were modified by incorporating actual motions derived from the IDE study. Motion parameters were based on:

- ISO 18192-1:
  - "the aim of the wear test method is to simulate average loading conditions rather than the extreme", and
  - "daily living activities are assumed to cover a certain percentage of the maximum range of motion with single events of higher loads and motions."
- Full active flexion-extension and lateral bending ROM for the PCM large footprint device at 2 years were independently assessed by a core radiographic laboratory. The 95th

percentile motions were used to provide a robust estimation of the population (the 95th percentile was also greater than 2 standard deviations from the mean).

- Literature analysis revealed that most activities of daily living (ADL) utilized 10-20% of the full active ROM. To be conservative, 50% of the full ROM was adopted. Axial rotation motion was based on worst-case (highest cross-shear) coupled motion reported by White and Panjabi[1] of 2° of coupled axial rotation for every 3° of lateral bending.
- The motion parameters are provided in ***Table 3***. Other wear testing parameters were as defined by ISO 18192-1.

Table 3: Clinically-Derived Motions for Wear Testing Based on ADLs of 50% of Full Active ROM (95th Percentile)

Motion	ADL ROM (50% of Full Active ROM) (degrees)
Flexion-Extension	6.5° (±3.25°)
Lateral Bending	3.5° (±1.75°)
Axial Rotation	2.3° (±1.17°)

B. Biocompatibility

The PCM Cervical Disc is composed of the following materials: cobalt chromium molybdenum (CoCrMo) endplates per ISO 5832-12; an ultra-high molecular weight polyethylene (UHMWPE) core per ISO 5834-1, ISO 5834-2 and ASTM F648; Titanium locking plate per ISO 5832-2 and ASTM F67; and titanium plasma spray (TPS) and calcium phosphate (CaP) coatings.

Biocompatibility testing was performed on the PCM Cervical Disc in their final sterilized state. Testing was conducted according to the requirements of ISO 10993-1, for the level and contact duration of a permanent implant contacting tissue and bone. The battery of biocompatibility tests conducted include: Cytotoxicity – MEM Elution (ISO 10993-5), Sensitization (ISO 10993-10), Intracutaneous Reactivity Test (Irritation) (ISO 10993-10), Acute Systemic Toxicity (ISO 10993-11), Genotoxicity – Ames Test (ISO 10993-3), and Genotoxicity – Chromosomal Aberration (ISO 10993-3). All test results met acceptance criteria demonstrating biocompatibility in line with the requirements of ISO 10993-1.

C. Sterilization and Shelf Life

A full sterilization validation has been conducted in accordance with ISO 11137-1, *Sterilization of health care products - Radiation - Part 1: Requirements for development validation and routine control of a sterilization process for medical devices.*

In order to validate the distribution and shelf-life of the PCM Cervical Disc, a distribution simulation and accelerated aging test has been conducted to support a five-year shelf life for the product.

X. SUMMARY OF CLINICAL STUDIES

Clinical data were collected in the United States under IDE G040081 to evaluate the safety and effectiveness of the PCM Cervical Disc. Data from this clinical study were the basis for the PMA approval decision. A summary of the pivotal clinical study is presented below.

A. Study Design and Objective

A prospective, multicenter, two-arm, randomized, concurrently controlled, non-inferiority clinical trial to compare the safety and effectiveness of the PCM Cervical Disc with anterior cervical discectomy and fusion (ACDF) with allograft and plate in treating patients with a degenerated cervical disc at one level from C3-C4 to C7-T1.

Clinical surgeries were performed during a period from January 19, 2005, to December 5, 2007. A total of 494 patients were enrolled at 24 investigational sites and 479 were treated in the clinical trial. Each investigational site was allowed to enroll a maximum of four patients in order for the investigators to become familiar with the implantation procedure for the PCM Cervical Disc.

Overall, 289 patients were treated with the PCM Cervical Disc (75 Training, 214 PCM) and 190 were treated with ACDF. Note, 1 Training PCM patient and 4 randomized PCM patients were intraoperatively switched to receive ACDF due to surgical reasons. The control group received a standard ACDF using the Synthes CSLP or DePuy Spine Slim-Loc System anterior cervical plate and structural allograft.

Among the 289 investigational patients treated in the IDE study, 198 received the PCM Standard device and 91 received the PCM-V device. The Sponsor was able to justify the poolability of the PCM Standard and PCM-V devices (see *Poolability Analysis* discussion). The various analyses were carried out on this subset cohort in addition to analyses on the all enrolled cohort. In PMA P100012, the applicant is only seeking marketing approval for the PCM-V.

The results and conclusions presented below represent updated data collected through September 2011.

Patients were evaluated preoperatively, intraoperatively, immediately postoperatively and then at 6 Weeks, 3 Months, 6 Months, 12 Months and 24 Months, and annually thereafter. The recommended postoperative care included a physical therapy program for non-impact exercises and active range of motion exercises. Patients were instructed to avoid repetitive cervical flexion and extension bending and lateral bending and rotation for 6 weeks following surgery.

All adverse events (implant-related or not) were monitored over the course of the trial and radiographic assessments were performed by an independent core laboratory. For the PMA, all adverse events were independently adjudicated (for adverse event code, severity and relationship to the device and/or procedure) by a Clinical Events Committee comprised of three board-certified spine surgeons.

The clinical trial used a non-inferiority study design, with a non-inferiority margin (delta) of 12.5%, to compare the overall success rate at 24 months postoperative between the PCM and ACDF groups. The primary overall success endpoint is a composite of several subcomponents, each of which must be a success in order for a patient to be deemed an overall success. Additional analyses were performed using a non-inferiority margin of 10% as requested by the Food and Drug Administration (FDA).

B. Study Population

The target population was comprised of patients with degenerated cervical discs and neurological symptoms at one level from C3 to T1. The study participants must have met the following inclusion/exclusion criteria:

Inclusion Criteria

To have qualified for enrollment in this study, patients must have met ***all*** of the inclusion criteria as follows:

- Age 18-65 years;
- Diagnosis of radiculopathy or myelopathy of the cervical spine, with either radiculopathy symptoms – pain, paresthesias, or paralysis in a specific nerve root distribution C4, C5, C6, C7, or C8, including at least one of the following: arm/shoulder pain (at least 30 mm on 100 mm VAS scale); decreased muscle strength of at least one level on the 0-5 scale; abnormal sensation, including hyperesthesia or hypoesthesia; and/or abnormal reflexes; or myelopathy symptoms including positive Romberg evaluation, abnormal heel/toe walk, pathologic hyperreflexia or clonus in lower extremity, positive Babinski, or positive Hoffman's;
- Symptomatic at only one level from C3-C4 to C7-T1;
- Radiographically determined pathology at level to be treated correlating to primary symptoms, including at least one of the following:
    - Decreased disc height compared to adjacent levels on radiographic film, CT, or MRI;
    - Degenerative spondylosis on CT or MRI;
    - Disc herniation on CT or MRI.
- Neck Disability Index (NDI) score ≥30% (15/50);
- Unresponsive to non-operative treatment for six weeks, or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment;
- Appropriate for treatment using an anterior surgical approach, including having no more than one previous anterior surgical approach to the cervical spine;
- Ability and willingness to comply with follow-up regimen; and
- Written informed consent given by patient or patient's legally authorized representative.

Exclusion Criteria

To have qualified for enrollment in this study, patients must have met ***none of*** the exclusion criteria as follows:

- Infection at the site of surgery;
- History of, or anticipated treatment for, active systemic infection, including HIV infection or hepatitis C;
- Prior attempted or completed cervical spine surgery, except (1) laminoforaminotomy, which includes removal of disc material necessary to perform a nerve root decompression, with less than one-third facetectomy at any level, or (2) a successful single-level anterior cervical fusion;
- More than one immobile vertebral level between C1-T1 from any cause, including but not limited to congenital abnormalities, osteoarthritic "spontaneous" fusions, and prior cervical spinal fusions;

- Previous trauma to the C3-T1 levels resulting in significant bony or disco-ligamentous cervical spine injury;
- Axial neck pain in the absence of other symptoms of radiculopathy or myelopathy justifying the need for surgical intervention;
- Radiographic confirmation of severe facet joint disease or degeneration.
- Osteoporosis: A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients to determine those patients who require a DEXA bone mineral density measurement. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score ≤ -2.5 (The World Health Organization definition of osteoporosis);
- Paget's disease, osteomalacia, or any other metabolic bone disease (excluding osteoporosis which is addressed above);
- Severe diabetes mellitus requiring daily insulin management;
- Active malignancy: a history of any invasive malignancy (except non-melanoma skin cancer), unless the patient has been treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 5 years;
- Tumor as source of symptoms;
- Symptomatic degenerative disc disease or significant cervical spondylosis at two or more levels;
- Marked cervical instability on resting lateral or flexion/extension radiographs demonstrated by:
  - Translation > 3.5 mm and/or;
  - > 11° angular difference to that of either adjacent level;
- Known or suspected allergy to cobalt, chromium, molybdenum, titanium, or polyethylene;
- Severe myelopathy to the extent that the patient is wheelchair bound;
- Congenital canal stenosis resulting in a canal diameter of < 10 mm, as measured by CT or MRI;
- Kyphotic segmental angulation of greater than 11° at treatment or adjacent levels;
- Arachnoiditis;
- Pregnant (verified in patients of childbearing potential by a negative urine pregnancy test when preadmission testing is obtained), or interested in becoming pregnant during the duration of the study;
- Autoimmune disorders that impact the musculoskeletal system (e.g., lupus, rheumatoid arthritis; ankylosing spondylitis);
- Congenital bony and/or spinal cord abnormalities that affect spinal stability;
- Spinal axis disease (thoracic or lumbar) to the extent that surgical consideration is likely anticipated within 6 months after the randomized cervical procedure;
- Other degenerative joint disease (e.g. shoulder, hip, knee) to the extent that surgical consideration is likely anticipated within 6 months after the randomized cervical procedure;
- Previous spine surgery within the 6 months preceding the randomized cervical procedure;
- Diseases or conditions that would preclude accurate clinical evaluation (e.g. neuromuscular disorders);
- Medications that could interfere with fusion or other bone/soft tissue healing (e.g. anticipated continued use of systemic steroid medication postoperatively);
- Currently experiencing acute episode of major mental illness (psychosis, major affective disorder, or schizophrenia), or manifesting physical symptoms without a diagnosable medical condition to account for the symptoms, which may indicate symptoms of psychological rather than physical origin;

- Current or recent history of substance abuse (drug or alcohol);
- Morbid obesity, defined as body mass index (BMI) > 40 or more than 100 lbs. over ideal body weight;
- Currently using, or planning to use, bone growth stimulators in the cervical spine;
- Use of any other investigational drug or medical device within the last 30 days prior to surgery
- Currently a prisoner; or
- Currently pursuing personal litigation (defined as litigation that will likely influence the patient's ability or willingness to accurately report their treatment outcomes) related to the neck or cervical spine injury; however, involvement in worker's compensation related litigation is not a required exclusion.

C. Sample Size Determination

This clinical study was based on a non-inferiority hypothesis that the primary overall success rate of the investigational PCM group was statistically non-inferior to the ACDF control group's rate. Based on Blackwelder's method[9] and assuming an overall success rate of 70% for both the PCM and ACDF groups, a 1.3:1 randomization ratio, a 12.5% non-inferiority margin (delta), a type I error of 5% (one-sided), and 80% power, the necessary sample size was determined to be 340 patients (192 PCM patients and 148 ACDF patients). Accounting for up to a 15% drop-out rate, loss to follow-up and small differences based on site-stratified randomization, the total sample size was upward adjusted to 416 patients (226 PCM patients and 190 ACDF patients). This sample size did not include the additional training patients. Analyses were conducted to adequately justify the poolability of the randomized PCM-V (N=81) and PCM Standard (N=133) sub-groups.

D. Study Evaluations

The protocol required each patient to remain in the study for 24 months postoperatively. In addition, all patients were required to return for annual follow-up visits until the last enrolled patient reached the 24 Months follow-up. The visit schedule and evaluations are summarized in ***Table 4***.

All radiographic endpoints were evaluated independently at a core laboratory by a board certified independent radiologist.

Table 4: Evaluation Summary and Visit Schedule

Evaluations	Preoperative (within 30 days prior to surgery)	Follow-Up Visit Windows					
		Post-Operative (7-21 days)	6 Weeks (± 2 wks)	3 Months (± 2 wks)	6 Months (± 2 wks)	12 Months (± 2 wks)	24 Months and Other Annual (± 2 wks)
Eligibility	x						
Demographics	x						
Medical History	x						
Medications	x	x	x	x	x	x	x
Neurological Assessment	x	x	x	x	x	x	x
Radiographic Evaluation	x	x	x	x	x	x	x
Neck Disability Index	x		x	x	x	x	x
Pain VAS	x		x	x	x	x	x
Dysphagia VAS	x		x	x	x	x	x

Bazaz Dysphagia	x		x	x	x	x	x
Nurick's Assessment	x		x	x	x	x	x
Odom's Criteria	x		x	x	x	x	x
SF-36	x		x	x	x	x	x
Employment Status	x		x	x	x	x	x
Patient Satisfaction						x	x
Adverse Events/ Surgical Intervention	x	x	x	x	x	x	x

E. Study Endpoints

The safety of the PCM was assessed by comparing the nature and frequency of adverse events (overall and in terms of severity and relationship to the device and/or procedure) and secondary surgical procedures as well as maintenance or improvement in neurological status to the ACDF control group.

The effectiveness of the PCM was assessed by evaluating improvement in the Neck Disability Index (NDI), neck and arm pain based on à Visual Analog Scale (VAS), and quality of life using the short-form 36 questionnaire (SF-36) as well as patient satisfaction compared to the ACDF control group.

In addition, several radiographic endpoints were considered in evaluating both safety and effectiveness, including range of motion, disc height, device displacement or migration, radiolucency, spinal fusion status, and heterotopic ossification.

Primary Endpoint – Overall Success

The primary endpoint of the study was individual patient overall success, a composite endpoint determined at 24 Months postoperative and defined as:

- Improvement of at least 20% on the Neck Disability Index (NDI) compared to baseline;
- No device failures requiring revision, reoperation, or removal; and
- Absence of major complications.

For the purpose of determining individual patient success, a major complication was defined as any of the following that are related to the PCM or ACDF device system or device component:

- Documented permanent neurologic damage or permanent nerve root injury related to the surgically treated level, defined as:
  - Decrease in one or more grades of motor strength or muscle atrophy,
  - New onset of reflex sympathetic dystrophy,
  - Persistent new onset of pathologic reflexes (Babinski, Hoffman, clonus, Romberg) present at 24 Months, or
  - Progression of paresthesia or anaesthesia in a specific cervical nerve root distribution;
- Vessel injury, bleeding, or hematoma requiring surgical intervention;
- Deep infection requiring surgical intervention (irrigation / debridement) or intravenous antibiotics;
- Spontaneous fusion of the treatment site (PCM patients only); or
- Failure of fusion of the treated level (ACDF patients only), defined as >2° of segmental movement on lateral flexion/extension x-rays and radiolucent lines at >50% of the graft-vertebra interfaces.

Secondary Endpoints

Secondary endpoints included:

- Time to recovery, defined as time to first achieve at least 20% improvement on NDI, sustained over all subsequent follow-up visits, as well as the following assessments at 24 Months compared to baseline
- Neck Pain VAS
- Arm Pain VAS
- Neurological status
- Spinal stability
- Disc height
- Quality of Life, SF-36
- Dysphagia VAS
- Bazaz dysphagia index
- Patient satisfaction
- Nurick's myelopathy assessment
- Displacement or migration of the device, graft or plate
- Radiolucency at the metal bone interface for the PCM
- Heterotopic ossification
- Adjacent segment degeneration
- Range of motion in flexion/extension at the operated level

Other Endpoints

Other endpoints included:

- Duration of hospitalization
- Blood loss
- Operative time

Safety Assessment

Information on all adverse events was collected during the course of the study.

F. Accountability of PMA Cohort

The patient accountability data are summarized in ***Table 5***, where training cases are referred to as the Training (TRN) group, the randomized investigational patients are referred to as the PCM group, and the randomized ACDF control patients are referred to as the ACDF group.

The follow-up rates are calculated from a maximum Per Protocol population of 75 Training, 211 PCM, and 184 ACDF patients. The patients evaluable for the primary composite overall success endpoint at 24 Months were 74.7%, 89.6% and 82.1% for the Training group, PCM group, and ACDF group, respectively.

Table 5: Patient Accountability

	12 Months (±2 Months)			24 Months (-3 Months, +6 Months)			36 Months (±6 Months)		
	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF
Enrolled/ITT	78	224	192	78	224	192	78	224	192
Not Treated	2	6	7	2	6	7	2	6	7
Treated (MITT)	76	218	185	76	218	185	76	218	185
Treated (Safety)	75	214	190	75	214	190	75	214	190
Deaths	0	1	0	0	1	0	0	1	0
Eligible Deviations	1	6	1	1	6	1	1	6	1
Not Yet Overdue	0	0	0	0	0	0	0	0	0
Per Protocol (Maximum)	75	211	184	75	211	184	75	211	184
Per Protocol (In Window)	66	202	162	56	189	153	46	180	141
Primary Endpoint (Protocol Defined)*	65	198	156	56	189	151	51	182	136
% Follow-up, Primary Endpoint (Protocol Defined)#	86.7%	93.8%	84.8%	74.7%	89.6%	82.1%	68.0%	86.3%	73.9%

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat.

* Number of patients evaluable for the primary composite overall success endpoint as defined in the protocol.

% Follow-up, Primary Endpoint = Primary Endpoint (Protocol Defined) / Per Protocol (Maximum).

The following flow diagram in ***Figure 2*** illustrates the origins of the analysis populations: Enrolled, Intent-to-Treat (ITT), Modified Intent-to-Treat (MITT), Per Protocol, Per Protocol In Window, and Safety.

The analysis populations are defined as follows:

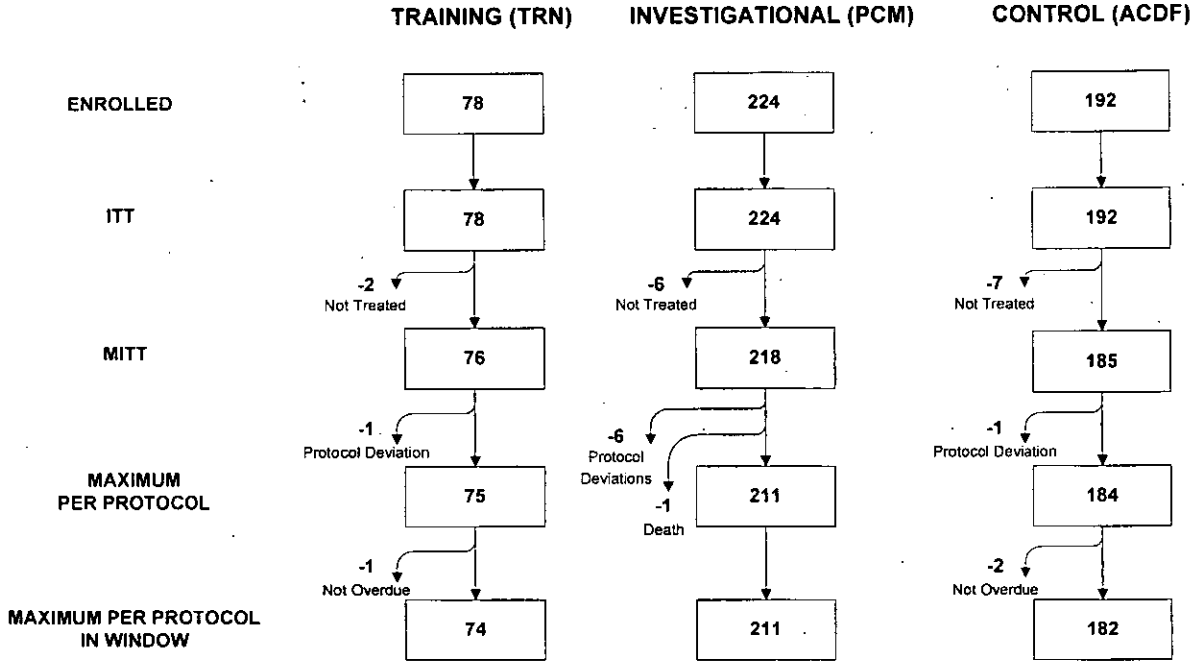
- Enrolled population includes any patient who gave Informed Consent and was enrolled. Analysis by group the patient was enrolled to.
- Intent-to-Treat (ITT) population includes any patient who was enrolled (Training) or randomized (PCM, ACDF). Analysis by group the patient was enrolled (Training) or randomized (PCM, ACDF) to.
- Modified Intent-to-Treat (MITT) population includes any patient who was treated. Analysis by group the patient was enrolled (Training) or randomized (PCM, ACDF) to.
- Per Protocol population includes any patient who was treated with the device they were randomized to, met the eligibility criteria, and had no major protocol violations. Analysis by group the patient was enrolled (Training) or randomized (PCM, ACDF) to.
- Per Protocol In Window population includes any patients who was treated with the device they were enrolled/randomized to, met the eligibility criteria, had no major protocol violations, and had a 24 Months visit within the visit window (i.e., 21 to 30 months). Analysis by group the patient was enrolled (Training) or randomized (PCM, ACDF) to.
- Safety population includes any patient who was treated. Analysis by group the patient was actually treated with (i.e., as-treated). The Safety population is the basis of the safety analyses.

Patient Demographics, Baseline Characteristics, and Surgical Characteristics were analyzed using both the MITT and Per Protocol In Window population.

The principal analysis of the primary endpoint was based on the Per Protocol population, with a visit window at 24 Months of -3 months to +6 months (e.g., 21 to 30 months). All primary endpoint statistical comparisons are made between the randomized PCM and ACDF groups. Analysis of the secondary endpoints was generally based on the Per Protocol In Window population, with statistical comparisons being made between the randomized group. The primary and select secondary endpoints were also analyzed using ITT and MITT population.

Sensitivity analyses were performed to assess the effect of covariates on the primary endpoint analysis. In addition, various imputation scenarios (e.g., Worst-Case) were performed to assess the potential effect of missing data on the primary endpoint analysis. Sub-group analyses were conducted to justify the poolability of the randomized PCM-V (N=81) and PCM Standard (N=133) cohorts.

Figure 2: Patient Accountability Flowchart



The data accounting for the protocol-required 24 Months clinical and radiographic assessments are tabulated in ***Table 6.***

Table 6: Patient Data Accounting at 24 Months

	Training	PCM	ACDF
Enrolled/ITT	78	224	192
Treated (MITT)	76	218	185
Treated (Safety; As-Treated)	75	214	190
Eligible Deviations	1	6	1
Deaths	0	1	0
Per Protocol (Maximum)	75	211	184
Per Protocol (In Window)	56	189	153
Clinical Assessments, n (%)*			
Neck Disability Index (NDI)	55 (73.3%)	187 (88.6%)	151 (82.1%)
VAS Neck and Arm Pain	55 (73.3%)	187 (88.6%)	150 (81.5%)
SF-36	54 (72.0%)	187 (88.6%)	151 (82.1%)
Patient Satisfaction	53 (70.7%)	182 (86.3%)	146 (79.3%)
Dysphagia	52 (69.3%)	187 (88.6%)	149 (81.0%)
Neurological Exam	54 (72.0%)	188 (89.1%)	153 (83.2%)
Radiographic Assessments, n (%)*			
Normal Disc Height	51 (68.0%)	182 (86.3%)	140 (76.1%)
Maintenance of Disc Height	50 (66.7%)	177 (83.9%)	135 (73.4%)
Radiolucency	51 (68.0%)	182 (86.3%)	152 (82.6%)
Migration	51 (68.0%)	182 (86.3%)	152 (82.6%)
ROM	53 (70.7%)	182 (86.3%)	151 (82.1%)
Dynamic Canal Stenosis	51 (68.0%)	182 (86.3%)	144 (78.3%)
Spine Stability	53 (70.7%)	182 (86.3%)	149 (81.0%)
Hypermobility	52 (69.3%)	181 (85.8%)	149 (81.0%)
Heterotopic Ossification	51 (68.0%)	182 (86.3%)	NA
Adjacent Segment Degeneration	41 (54.7%)	147 (69.7%)	119 (64.7%)

ITT = Intent-to-Treat.; MITT = Modified Intent-to-Treat.

* Percentage are based on the Per Protocol (Maximum) patient population.

G. Patient Demographics and Baseline Parameters

The demographics of the study population are typical for a cervical artificial disc study conducted in the US. Demographic data and preoperative evaluations for all patients enrolled and treated in the study are included in ***Table 7*** and ***Table 8***.

Table 7: Patient Demographics and Baseline Characteristics (Modified Intent-to-Treat Population)

	Training (N=76)	PCM (N=218)	ACDF (N=185)	P-Value*
Age, mean (SD) years	42.2 (8.2)	45.3 (9.0)	43.7 (8.3)	0.059 (b)
Female, no. (%)	29 (38.2%)	105 (48.2%)	89 (48.1%)	0.991 (a)
Race, no. (%)				
Caucasian	70 (92.1%)	202 (92.7%)	170 (91.9%)	0.145 (a)
Black	2 (2.6%)	10 (4.6%)	7 (3.8%)	
Asian	0 (0.0%)	0 (0.0%)	5 (2.7%)	
Hispanic	3 (3.9%)	3 (1.4%)	2 (1.1%)	
Other	1 (1.3%)	3 (1.4%)	1 (0.5%)	
Height, mean (SD) inches	68.3 (4.4)	67.4 (4.2)	67.3 (3.8)	0.737 (b)
Weight, mean (SD) pounds	186.0 (40.2)	182.9 (39.9)	177.1 (38.8)	0.143 (b)
BMI, mean (SD) kg/m^2	28.0 (4.9)	28.2 (4.6)	27.3 (4.8)	0.079 (b)
Current Tobacco Use, no. (%)	39 (51.3%)	113 (51.8%)	90 (48.6%)	0.524 (a)
History Nonoperative Care, no. (%)				
Medication Used	73 (96.1%)	210 (96.3%)	181 (97.8%)	0.558 (c)
Injections	34 (44.7%)	117 (53.7%)	80 (43.2%)	0.045 (c)
Physical Therapy	54 (71.1%)	157 (72.0%)	126 (68.1%)	0.444 (c)
Brace	5 (6.6%)	24 (11.0%)	25 (13.5%)	0.449 (c)
Chiropractic	24 (31.6%)	66 (30.3%)	75 (40.5%)	0.036 (c)
Other	20 (26.3%)	33 (15.1%)	39 (21.1%)	0.151 (c)
History Prior Surgery, no. (%)				
Lamino-foraminotomy without Facetectomy	2 (2.6%)	1 (0.5%)	3 (1.6%)	0.337 (c)
Lamino-foraminotomy with Facetectomy	0 (0.0%)	1 (0.5%)	4 (2.2%)	0.184 (c)
Fusion	14 (18.4%)	29 (13.3%)	20 (10.8%)	0.541 (c)
Neurological Symptoms, no. (%)				
Radiculopathy and Myelopathy	11 (14.5%)	33 (15.1%)	45 (24.3%)	0.023 (c)
Radiculopathy Only	65 (85.5%)	184 (84.4%)	140 (75.7%)	
Myelopathy Only	0 (0.0%)	1 (0.4%)	0 (0.0%)	
Radiographic Findings, no. (%)				
Herniated Nucleus Pulposus	66 (86.8%)	176 (80.7%)	155 (83.8%)	0.437 (c)
Spondylosis	11 (14.5%)	41 (18.8%)	28 (15.1%)	0.355 (c)
Loss of Disc Height	16 (21.1%)	39 (17.9%)	53 (28.6%)	0.012 (c)

Note: Percentages are based on total number of patients for each treatment group.

* Comparing PCM and ACDF (two-sided): (a) Chi-squared test; (b) t-test; (c) Fisher's exact test. P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

Preoperative clinical and radiographic endpoints, including Neck Disability Index (NDI) scores, Visual Analog Scale (VAS) Neck Pain, VAS Arm Pain (left, right, worst arm), SF-36 (Physical Component Score [PCS] and Mental Component Score [MCS]), neurological status, and index level range of motion (ROM) and translation, are shown in ***Table 8***.

Based on the baseline evaluations, it was concluded that the randomization was successful and the PCM and ACDF groups were similar and well balanced.

Table 8: Baseline Evaluation of Clinical Endpoints (Per Protocol 24 Months In Window Population)

Endpoint	Training (N=56)	PCM (N=189)	ACDF (N=153)	P-Value*
Neck Disability Index (NDI)	51.2 (13.8)	55.8 (14.5)	54.7 (14.0)	0.470 (a)
VAS Neck Pain, mm	66.8 (24.5)	68.4 (22.3)	73.5 (18.6)	0.076 (a)
VAS Right Arm Pain, mm	49.3 (34.3)	47.9 (33.7)	50.6 (33.4)	0.625 (a)
VAS Left Arm Pain, mm	43.0 (36.7)	51.2 (33.9)	50.0 (32.6)	0.679 (a)
VAS Worst Arm Pain, mm	74.9 (17.3)	73.4 (19.4)	74.4 (18.2)	0.791 (a)
SF-36 PCS	36.3 (6.3)	34.4 (6.8)	34.6 (6.3)	0.681 (b)
SF-36 MCS	43.0 (12.7)	43.3 (12.3)	41.9 (11.4)	0.303 (b)
Neurological Status, no. (%)				
Motor (normal)	18 (32.1%)	63 (33.3%)	57 (37.3%)	0.495 (c)
Sensory (normal)	24 (42.9%)	87 (46.0%)	68 (44.4%)	0.827 (c)
Reflexes (normal)	49 (87.5%)	167 (88.4%)	124 (81.0%)	0.068 (c)
Range of Motion, degrees	7.9 (4.5)	7.9 (4.7)	7.8 (4.4)	0.910 (b)
Translation, mm	0.8 (0.5)	0.9 (0.6)	0.9 (0.7)	0.470 (b)

Note: Continuous variables are reported as means and standard deviations.

* Comparing PCM and ACDF (two-sided): (a) Mann-Whitney-Wilcoxon rank sum test; (b) t-test; (c) Fisher's exact test. P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

H. Surgical and Hospitalization Parameters

Typical operative characteristics including surgical time, blood loss, and length of hospital stay are reported in ***Table 9***. There were differences between the groups in mean surgical time, at 100.8 minutes (SD 42.0) in the PCM group, compared to 85.7 (SD 40.5) minutes in the control group. The average 15.1 minute difference may be explained by differences in disc space preparation surgical technique associated with the surgeons learning a new procedure. The mean surgical time of the Training group alone was 127.6 minutes (SD 47.5).

The amount of blood loss was comparable between groups with 65.6 mL for PCM and 58.6 mL for ACDF. The average length of hospital stay was shorter in the PCM group at 1.2 days (range 0-3) compared to the ACDF group at 1.4 days (range 0-6). Similar and comparable results were obtained when the analysis was performed on the Per Protocol In Window population.

Table 9: Surgical Data
(Modified Intent-to-Treat Population)

	Training (N=76)	PCM (N=218)	ACDF (N=185)
Treated Level, no. (%)			
C3-C4	1 (1.3%)	0 (0.0)%	8 (4.3%)
C4-C5	5 (6.6%)	31 (14.2%)	17 (9.2%)
C5-C6	33 (43.4%)	109 (50.0%)	98 (53.0%)
C6-C7	35 (46.1%)	76 (34.9%)	62 (33.5%)
C7-T1	2 (2.6%)	2 (0.9%)	0 (0.0%)
Surgery Time, mean (SD) min	126.7 (45.6)	100.8 (42.0)	85.7 (40.5)
Blood Loss, mean (SD) mL	82.5 (58.5)	65.6 (48.3)	58.6 (46.1)
Hospitalization, mean (SD) days	1.3 (0.6)	1.2 (0.6)	1.4 (0.7)

In the PCM group, a conventional discectomy was performed to remove the disc and accomplish neural decompression, and the disc space was then prepared to receive the PCM implant. The depth and width of the disc space were measured, and PCM trial sizers were used to maximize endplate coverage and select the appropriate implant footprint. This was verified radiographically. In the clinical study, the Small PCM was implanted in 18.7% of patients, Medium PCM in 46.3%, and Large PCM in 35.0%. The selected PCM heights were 6.5 mm in 76.8%, 7.2 mm in 6.2%, and 8.0 mm in 17.0% of patients. The PCM Standard was used in 68.6% of cases and the PCM-V was used in 31.4%.

Table 10: PCM Implants Used
(Safety Population; N=289)

Height	Small (14mm × 17mm)	Medium (16mm × 17mm)	Large (17mm × 20mm)
Standard (n=198), no. (%)			
6.5 mm	26 (9.0%)	77 (26.6%)	48 (16.7%)
8.0 mm	6 (2.1%)	15 (5.2%)	26 (9.0%)
V-Teeth (n=91), no. (%)			
6.5 mm	22 (7.6%)	33 (11.4%)	16 (5.5%)
7.2 mm	0 (0.0%)	7 (2.4%)	11 (3.8%)
8.0 mm	0 (0.0%)	2 (0.7%)	0 (0.0%)

Note: Percentages (%) are based on PCM Safety population (combined Training and PCM).

I. Safety and Effectiveness Results

1) Safety Results

The safety of the investigational treatment was assessed based on the Safety (as-treated) population of 479 patients (75 Training, 214 PCM, and 190 ACDF). One Training patient and 4 PCM patients were intraoperatively switched to the ACDF procedure. In the following safety analyses, they are classified in the ACDF group.

As of September 2011, the average follow-up time for the Training, PCM, and ACDF groups were 5.7 years, 5.1 years, and 4.9 years, respectively.

All Adverse Events (AEs) were classified as Serious Adverse Events (SAEs), Subsequent Secondary Surgical Interventions (SSSIs), or Unanticipated Adverse Device Effects (UADE), according to the protocol definitions. A Clinical Events Committee (CEC) was utilized during the course of the PCM study to provide an expert assessment of study safety data. Details pertaining to the adverse event categories are provided in Section XVI.

a) Adverse Events

The definitions for the adverse event categories are provided below:

Category	Definition
Implant Related Events - Related or possibly related to the implant	
Adjacent Level Disease	Onset of degeneration or spinal disease at a level adjacent to the implant.
Implant Displacement/Loosening	Migration or loosening of the implant.
Malpositioned Implant	Improper placement of the implant.
Neck/Arm Pain	Pain in the neck and/or arm.
Non-union	Failure of the vertebral bodies to fuse at the treated level.
Other	Other events not defined, includes implant related headaches and implant noise.
Radiolucency	Transparency of the bony structures surrounding the implant.
Spinal Event	Degeneration or disease of the spine, including bone growth and stenosis.
Subsidence	Events associated with implant subsidence into the vertebral bone.
Trauma	Damage inflicted on the body as the direct or indirect result of an external force.
Surgery Related Events - Related or possibly related to the surgical procedure	
Dysphagia/Dysphonia	Difficulty swallowing or speaking.
Gastrointestinal	Ailments relating to or affecting the stomach or intestines.
Incision Site	Events associated with the surgical incision site.
Infection	Ailments associated with an infectious agent.
Neck/Arm Pain	Events primarily associated with reports of neck and/or arm pain.
Neurologic	Conditions related to or potentially related to the neurological system.
Other	Events or unknown etiology or that cannot be readily classified into other criteria
Respiratory	Ailments or symptoms associated with respiration or the respiratory system.
Spinal Event	Events or conditions associated with the spine.
Urogenital	Conditions relating to or affecting the organs or functions of excretion and reproduction.
Vertebral Fracture	Fractures of the vertebra.
Systemic Events - Unrelated to the device or surgical procedure	
Cardiac Events	Any condition primarily associated with the heart and/or vascular system.
Dysphagia/Dysphonia	Difficulty swallowing or speaking.
Gastrointestinal	Ailments relating to or affecting the stomach or intestines.
Infection	Ailments associated with an infectious agent.
Mental Disorder	Ailments or disorders of a psychiatric nature or origin.
Musculoskeletal Trauma	Conditions pertaining to the muscles and skeleton, such as fracture, ligament tear, arthritis of any kind, and degenerative conditions, excluding muscle spasms and events related to spinal degenerative conditions
Musculoskeletal/Adjacent Level Disease	Conditions pertaining to the muscles and skeleton associated with Adjacent Level Disease of the spine
Musculoskeletal/Back/Leg Pain	Conditions pertaining to the muscles and skeleton primarily associated with reports of back and/or leg pain.
Musculoskeletal/Neck/Arm Pain	Conditions pertaining to the muscles and skeleton primarily associated with reports of neck and/or arm pain.
Musculoskeletal/Other	Conditions pertaining to the muscles and skeleton of unknown etiology or that cannot be readily be classified in another category.
Musculoskeletal/Spinal Event	Conditions pertaining to the muscles and skeleton primarily associated with the spine.
Neurologic	Conditions related to or potentially related to the neurological system.
Other	Events or unknown etiology or that cannot be readily classified into other criteria.
Other Trauma	Traumatic events associated with symptoms not identified in any other category.
Respiratory	Ailments or symptoms associated with respiration or the respiratory system.
Urogenital	Conditions relating to or affecting the organs or functions of excretion and reproduction.

A summary of all adverse events is shown in ***Table 11***. There were a total of 226 AEs in the Training group, 507 AEs in the PCM group, and 484 AEs in the ACDF group.

Table 11: Summary of Adverse Events (Safety Population)

Category	Counts	Training (N=75)	PCM (N=214)	ACDF (N=190)	P-Value*
All Adverse Events (AEs)	Patients (%)	59 (79%)	180 (84%)	163 (86%)	0.678
	Events (E/pt)	226 (3.0)	507 (2.4)	484 (2.6)	
Implant-Related AEs	Patients (%)	26 (35%)	29 (14%)	44 (23%)	0.014
	Events (E/pt)	35 (0.5)	33 (0.2)	54 (0.3)	
Surgery-Related AEs	Patients (%)	23 (31%)	59 (28%)	67 (35%)	0.107
	Events (E/pt)	35 (0.5)	79 (0.4)	97 (0.5)	
Serious Adverse Events (SAEs)	Patients (%)	23 (31%)	68 (32%)	57 (30%)	0.747
	Events (E/pt)	51 (0.7)	95 (0.4)	86 (0.5)	
AEs within 48 Hours of Surgery	Patients (%)	12 (16%)	31 (14%)	26 (14%)	0.887
	Events	15 (0.2)	32 (0.2)	35 (0.2)	
Device Failures (Revision, Reoperation, Removal, or Supplemental Fixation)	Patients (%)	9 (12%)	16 (7%)	14 (7%)	1.000
	Events (E/pt)	11 (0.1)	16 (0.1)	14 (0.1)	

Note: 1. Adverse Events (AEs) based on cumulative AE database as of September 2011.
2. Percentages and events/patients are based on total number of patients for each treatment group.
* Comparing PCM and ACDF based on Fisher's exact test (two-sided). P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

Table 12 lists the adverse events by category for the All PCM group (Training and PCM) and the ACDF group.

Table 12: All Adverse Events (Safety Population)

Adverse Event	Intraop (0 - 2 Days)		Periop (>2 Days -6 Wks.)		Short Term (>6 Wks. - 12 Mon.)		Long Term (>12 - 24 Mon.)		Longer Term (>24 Mon.)		All PCM (N=289)		ACDF (N=190)	
	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	Pts (%)	Events (E/Pt)	Pts (%)	Events (E/Pt)
All Adverse Events	**47**	**35**	**78**	**40**	**182**	**120**	**179**	**138**	**247**	**151**	**239 (82.7%)**	**733 (2.54)**	**163 (85.8%)**	**484 (2.55)**
Implant Related - Adjacent Level Disease	0	0	0	0	4	5	2	17	3	7	9 (3.1%)	9 (0.03)	27 (14.2%)	29 (0.15)
Implant Related - Implant Displacement/Loosening	0	0	2	0	8	1	6	0	6	0	22 (7.6%)	22 (0.08)	1 (0.5%)	1 (0.01)
Implant Related - Malpositioned Implant	0	0	0	0	0	0	1	0	0	0	1 (0.3%)	1 (<0.01)	0 (0.0%)	0 (0.00)
Implant Related - Neck/Arm Pain	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0 (0.00)	1 (0.5%)	1 (0.01)
Implant Related - Non-union	0	0	0	0	0	2	0	8	0	2	0 (0.0%)	0 (0.00)	11 (5.8%)	12 (0.06)
Implant Related - Other	0	0	0	0	0	1	0	0	1	0	1 (0.3%)	1 (<0.01)	1 (0.5%)	1 (0.01)
Implant Related - Radiolucency	0	0	0	0	5	0	4	2	0	1	9 (3.1%)	9 (0.03)	3 (1.6%)	3 (0.02)
Implant Related - Spinal Event	1	0	1	0	3	0	9	2	7	2	20 (6.9%)	21 (0.07)	4 (2.1%)	4 (0.02)
Implant Related - Subsidence	0	0	1	1	1	1	0	0	1	0	3 (1.0%)	3 (0.01)	2 (1.1%)	2 (0.01)
Implant Related - Trauma	0	0	0	0	0	1	1	0	1	0	2 (0.7%)	2 (0.01)	1 (0.5%)	1 (0.01)
Surgery Related - Dysphagia/Dysphonia	5	10	8	1	5	8	3	3	3	6	22 (7.6%)	24 (0.08)	23 (12.1%)	28 (0.15)
Surgery Related - Gastrointestinal	2	2	1	0	0	0	0	0	0	0	3 (1.0%)	3 (0.01)	2 (1.1%)	2 (0.01)
Surgery Related - Incision Site	4	0	7	3	3	0	1	1	0	0	14 (4.8%)	15 (0.05)	4 (2.1%)	4 (0.02)
Surgery Related - Infection	0	0	1	1	0	0	0	0	0	0	1 (0.3%)	1 (<0.01)	1 (0.5%)	1 (0.01)
Surgery Related - Neck/Arm Pain	5	4	11	5	18	14	8	9	5	3	37 (12.8%)	47 (0.16)	32 (16.8%)	35 (0.18)
Surgery Related - Neurologic	2	3	2	2	2	1	6	3	3	1	14 (4.8%)	15 (0.05)	10 (5.3%)	10 (0.05)
Surgery Related - Other	5	3	0	2	0	2	0	0	0	0	5 (1.7%)	5 (0.02)	7 (3.7%)	7 (0.04)
Surgery Related - Respiratory	1	0	0	0	0	0	0	0	0	0	1 (0.3%)	1 (<0.01)	0 (0.0%)	0 (0.00)

Adverse Event	Intraop (0 - 2 Days)		Periop (>2 Days -6 Wks.)		Short Term (>6 Wks. - 12 Mon.)		Long Term (>12 - 24 Mon.)		Longer Term (>24 Mon.)		All PCM (N=289)		ACDF (N=190)	
	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	All PCM	ACDF	Pts (%)	Events (E/Pt)	Pts (%)	Events (E/Pt)
Surgery Related - Spinal Event	0	1	0	0	1	1	0	4	1	2	2 (0.7%)	2 (0.01)	8 (4.2%)	8 (0.04)
Surgery Related - Urogenital	0	1	0	1	0	0	0	0	0	0	0 (0.0%)	0 (0.00)	2 (1.1%)	2 (0.01)
Surgery Related - Vertebral Fracture	1	0	0	0	0	0	0	0	0	0	1 (0.3%)	1 (<0.01)	0 (0.0%)	0 (0.00)
Systemic - Cardiac Events	3	2	1	1	2	1	3	2	4	0	12 (4.2%)	13 (0.04)	6 (3.2%)	6 (0.03)
Systemic - Dysphagia/Dysphonia	0	0	0	0	2	0	1	4	1	0	3 (1.0%)	4 (0.01)	4 (2.1%)	4 (0.02)
Systemic - Gastrointestinal	2	0	2	1	6	2	5	1	3	2	14 (4.8%)	18 (0.06)	6 (3.2%)	6 (0.03)
Systemic - Infection	0	2	2	2	1	0	4	2	15	8	19 (6.6%)	22 (0.08)	12 (6.3%)	14 (0.07)
Systemic - Mental Disorder	0	1	0	0	1	0	1	2	2	1	4 (1.4%)	4 (0.01)	4 (2.1%)	4 (0.02)
Systemic - Musculoskeletal Trauma	1	0	4	2	15	16	20	12	35	16	59 (20.4%)	75 (0.26)	32 (16.8%)	46 (0.24)
Systemic - Musculoskeletal/Adjacent Level Disease	0	1	0	0	1	0	0	0	1	0	2 (0.7%)	2 (0.01)	1 (0.5%)	1 (0.01)
Systemic - Musculoskeletal/Back/Leg Pain	0	0	1	1	20	7	16	10	25	16	47 (16.3%)	62 (0.21)	33 (17.4%)	34 (0.18)
Systemic - Musculoskeletal/Neck/Arm Pain	1	0	13	9	54	36	35	15	41	36	114 (39.4%)	144 (0.50)	68 (35.8%)	96 (0.51)
Systemic - Musculoskeletal/Other	1	1	4	0	6	4	15	5	23	8	37 (12.8%)	49 (0.17)	17 (8.9%)	18 (0.09)
Systemic - Musculoskeletal/Spinal Event	0	0	1	1	3	4	12	6	21	14	36 (12.5%)	37 (0.13)	22 (11.6%)	25 (0.13)
Systemic - Neurologic	2	0	4	2	6	9	6	11	7	9	23 (8.0%)	25 (0.09)	27 (14.2%)	31 (0.16)
Systemic – Other	7	3	5	4	14	3	15	13	31	12	57 (19.7%)	72 (0.25)	26 (13.7%)	35 (0.18)
Systemic - Other Trauma	3	0	3	1	1	0	1	1	1	0	9 (3.1%)	9 (0.03)	2 (1.1%)	2 (0.01)
Systemic - Respiratory	0	0	2	0	0	0	3	1	1	1	4 (1.4%)	6 (0.02)	2 (1.1%)	2 (0.01)
Systemic - Urogenital	1	1	2	0	0	1	1	4	5	3	7 (2.4%)	9 (0.03)	8 (4.2%)	9 (0.05)

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

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The cumulative number and incidence rates for each adverse event category were compared between the PCM and ACDF groups in ***Table 13*** which also reports unadjusted p-values (two-sided). As a result of multiplicity, caution should be used when making statistical inferences regarding difference in incidence rates.

Adverse events that occurred in greater than 5% of the patients in the PCM group included Implant-Related Spinal Event (5.1%), Surgery-Related Dysphagia/Dysphonia (6.5%), Surgery-Related Incision Site (5.6%), Surgery-Related Neck/Arm Pain (9.8%), Surgery-Related Neurologic (5.6%), Systemic Gastrointestinal (5.6%), Systemic Infection (7.0%), Musculoskeletal Trauma (19.6%), Musculoskeletal Back/Leg Pain (16.8%), Musculoskeletal Other (13.6%), Musculoskeletal Spinal Event (15.0%), Musculoskeletal Neurologic (5.6%), and Systemic Other (19.6%).

Adverse events that occurred in greater than 5% of the patients in the ACDF group included Implant-Related Adjacent Level Disease (14.2%), Implant-Related Non-Union (5.8%), Surgery-Related Dysphagia/Dysphonia (12.1%), Surgery-Related Neck Arm Pain (16.8%), Surgery-Related Neurologic (5.3%), Systemic Infection (6.3%), Musculoskeletal Trauma (16.8%), Musculoskeletal Back/Leg Pain (17.4%), Musculoskeletal Neck/Arm Pain (35.8%), Musculoskeletal Other (8.9%), Musculoskeletal Spinal Event (11.6%), Musculoskeletal Neurologic (14.2%), and Systemic Other (13.7%).

Table 13: Comparison of Adverse Events (Safety Population)

Adverse Event	Patients Experiencing Adverse Events (%)		P-Value*
	PCM (N=214)	ACDF (N=190)	
All Adverse Event	**180 (84.1%)**	**163 (85.8%)**	**0.678**
Implant Related - Adjacent Level Disease	5 (2.3%)	27 (14.2%)	< 0.001
Implant Related - Implant Displacement/Loosening	10 (4.7%)	1 (0.5%)	0.012
Implant Related - Neck/Arm Pain	0 (0.0%)	1 (0.5%)	0.470
Implant Related - Non-union	0 (0.0%)	11 (5.8%)	< 0.001
Implant Related - Other	1 (0.5%)	1 (0.5%)	1.000
Implant Related - Radiolucency	3 (1.4%)	3 (1.6%)	1.000
Implant Related - Spinal Event	11 (5.1%)	4 (2.1%)	0.121
Implant Related - Subsidence	1 (0.5%)	2 (1.1%)	0.603
Implant Related - Trauma	1 (0.5%)	1 (0.5%)	1.000
Surgery Related - Dysphagia/Dysphonia	14 (6.5%)	23 (12.1%)	0.059
Surgery Related - Gastrointestinal	2 (0.9%)	2 (1.1%)	1.000
Surgery Related - Incision Site	12 (5.6%)	4 (2.1%)	0.079
Surgery Related - Infection	1 (0.5%)	1 (0.5%)	1.000
Surgery Related - Neck/Arm Pain	21 (9.8%)	32 (16.8%)	0.040
Surgery Related - Neurologic	12 (5.6%)	10 (5.3%)	1.000
Surgery Related - Other	4 (1.9%)	7 (3.7%)	0.361
Surgery Related - Respiratory	1 (0.5%)	0 (0.0%)	1.000
Surgery Related - Spinal Event	2 (0.9%)	8 (4.2%)	0.511
Surgery Related - Urogenital	0 (0.0%)	2 (1.1%)	0.221
Surgery Related - Vertebral Fracture	1 (0.5%)	0 (0.0%)	1.000
Systemic - Cardiac Events	7 (3.3%)	6 (3.2%)	1.000
Systemic - Dysphagia/Dysphonia	2 (0.9%)	4 (2.1%)	0.426
Systemic - Gastrointestinal	12 (5.6%)	6 (3.2%)	0.334
Systemic - Infection	15 (7.0%)	12 (6.3%)	0.844
Systemic - Mental Disorder	2 (0.9%)	4 (2.1%)	0.426
Systemic - Musculoskeletal Trauma	42 (19.6%)	32 (16.8%)	0.520
Systemic - Musculoskeletal/Adjacent Level Disease	2 (0.9%)	1 (0.5%)	1.000
Systemic - Musculoskeletal/Back/Leg Pain	36 (16.8%)	33 (17.4%)	0.895
Systemic - Musculoskeletal/Neck/Arm Pain	87 (40.7%)	68 (35.8%)	0.356
Systemic - Musculoskeletal/Other	29 (13.6%)	17 (8.9%)	0.160
Systemic - Musculoskeletal/Spinal Event	32 (15.0%)	22 (11.6%)	0.380
Systemic - Neurologic	12 (5.6%)	27 (14.2%)	0.004
Systemic – Other	42 (19.6%)	26 (13.7%)	0.143
Systemic - Other Trauma	6 (2.8%)	2 (1.1%)	0.291
Systemic - Respiratory	3 (1.4%)	2 (1.1%)	1.000
Systemic - Urogenital	2 (0.9%)	8 (4.2%)	0.051

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

* Comparing PCM and ACDF based on Fisher's exact test (two-sided). P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

Implant-related adverse events are shown in ***Table 14***. Implant-related AEs with an incidence rate greater than 5% were spinal events (5.1%) in the PCM group, and adjacent level disease (14.2%) and non-union (5.8%) in the ACDF group. In addition, implant displacement/loosening occurred at a rate of 4.7% in the PCM group.

Table 14: Implant-Related Adverse Events
(Safety Population)

Adverse Event	Intraop (0 - 2 Days)		Periop (>2 Days - 6 Wks.)		Short Term (>6 Wks. - 12 Mon.)		Long Term (>12 - 24Mon.)		Longer Term (>24 Mon.)		PCM (N=214)	ACDF (N=190)
	PCM	ACDF	PCM	ACDF	PCM	ACDF	PCM	ACDF	PCM	ACDF	Patients (%)	Patients (%)
Implant Related - Adjacent Level Disease	0	0	0	0	2	5	2	17	1	7	5 (2.3%)	27 (14.2%)
Implant Related - Implant Displacement/Loosening	0	0	1	0	3	1	1	0	5	0	10 (4.7%)	1 (0.5%)
Implant Related - Neck/Arm Pain	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.5%)
Implant Related - Non-union	0	0	0	0	0	2	0	8	0	2	0 (0.0%)	11 (5.8%)
Implant Related - Other	0	0	0	0	0	1	0	0	1	0	1 (0.5%)	1 (0.5%)
Implant Related - Radiolucency	0	0	0	0	3	0	0	2	0	1	3 (1.4%)	3 (1.6%)
Implant Related - Spinal Event	1	0	0	0	0	0	6	2	5	2	11 (5.1%)	4 (2.1%)
Implant Related - Subsidence	0	0	1	1	0	1	0	0	0	0	1 (0.5%)	2 (1.1%)
Implant Related - Trauma	0	0	0	0	0	1	0	0	1	0	1 (0.5%)	1 (0.5%)

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

As shown in ***Table 15***, there were 27.6% of patients who experienced surgery-related AEs in the PCM group and 36.8% in the ACDF group. Surgery-related AEs that occurred at an incidence rate greater than 5% were: neck/arm pain (9.8%), dysphagia/dysphonia events (6.5%), neurologic (5.6%), incision site (5.6%) in the PCM group; and neck/arm pain (16.8%), dysphagia/dysphonia (12.1%), neurologic (5.3%) in the ACDF group.

Table 15: Surgery-Related Adverse Events (Safety Population)

Adverse Event	PCM (N=214)		ACDF (N=190)	
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
Surgery-Related Adverse Event	**59 (27.6%)**	**79 (0.37)**	**70 (36.8%)**	**97 (0.51)**
Surgery Related - Dysphagia/Dysphonia	14 (6.5%)	15 (0.07)	23 (12.1%)	28 (0.15)
Surgery Related - Gastrointestinal	2 (0.9%)	2 (0.01)	2 (1.1%)	2 (0.01)
Surgery Related - Incision Site	12 (5.6%)	13 (0.06)	4 (2.1%)	4 (0.02)
Surgery Related - Infection	1 (0.5%)	1 (<0.01)	1 (0.5%)	1 (0.01)
Surgery Related - Neck/Arm Pain	21 (9.8%)	27 (0.13)	32 (16.8%)	35 (0.18)
Surgery Related - Neurologic	12 (5.6%)	13 (0.06)	10 (5.3%)	10 (0.05)
Surgery Related - Other	4 (1.9%)	4 (0.02)	7 (3.7%)	7 (0.04)
Surgery Related - Respiratory	1 (0.5%)	1 (<0.01)	0 (0.0%)	0 (0.00)
Surgery Related - Spinal Event	2 (0.9%)	2 (0.01)	8 (4.2%)	8 (0.04)
Surgery Related - Urogenital	0 (0.0%)	0 (0.00)	2 (1.1%)	2 (0.01)
Surgery Related - Vertebral Fracture	1 (0.5%)	1 (<0.01)	0 (0.0%)	0 (0.00)

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

The cumulative totals of adverse events related to pain are tabulated in ***Table 16***. Over 62% of patients reported at least one AE related to pain in patients with more than one pain AE and in the total number of pain AEs. There were no significant differences between groups except for the "Other" category which included fibromyalgia, myofascial pain syndrome, jaw pain, kidney stones, corneal abrasion, and other miscellaneous non-spine related reports of pain.

Table 16: Summary of Pain Adverse Events (Safety Population)

Category	TRN (N=75)	PCM (N=214)	ACDF (N=190)	P-Value*
Patients with ≥1 Pain AE	47 (62.7%)	132 (61.7%)	120 (63.2%)	0.837 (a)
Total Number of Pain AEs (AEs/Patient)	104 (1.39)	264 (1.23)	232 (1.22)	0.909 (b)
Pain AEs by Location (AEs/Patient)				
Neck Only	26 (0.35)	64 (0.30)	56 (0.29)	0.937 (b)
Arm Only	29 (0.39)	64 (0.30)	68 (0.36)	0.303 (b)
Neck and Arm	14 (0.19)	35 (0.16)	42 (0.22)	0.188 (b)
Headache	5 (0.07)	12 (0.06)	9 (0.05)	0.702 (b)
Back and/or Lower Extremity	21 (0.28)	69 (0.32)	52 (0.27)	0.372 (b)
Other	9 (0.12)	20 (0.09)	5 (0.03)	0.011 (b)

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

* Comparing PCM and ACDF (two-sided): (a) Fisher's exact test; (b) Chi-squared test (rate ratio). P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

The number and relative frequency of adverse events by treatment level is presented in ***Table 17***. These reflect the number of patients who experienced an AE relative to the number of patients treated at that level within each group. There are no statistical differences in the incidence of adverse events between the PCM and ACDF groups at the treated levels.

Table 17: Adverse Events by Level Treated (Patient Counts) (Safety Population)

Level Treated	Training (N=75)	PCM (N=214)	ACDF (N=190)	P-Value*
C3-4	1 (100%)	0	8 (100%)	NA
C4-5	5 (100%)	27 (90%)	16 (89%)	1.000
C5-6	26 (79%)	93 (87%)	84 (84%)	0.561
C6-7	26 (76%)	59 (79%)	55 (86%)	0.376
C7-T1	1 (50%)	1 (50%)	0	NA
Total	59 (79%)	180 (84%)	163 (86%)	0.678

Note: 1. Adverse Events (AEs) based on cumulative AE database as of September 2011.
2. Percentages are based on total number of patients treated at the reported level for each treatment group.
* Comparing PCM and ACDF based on Fisher's exact test (two-sided). P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance. NA as a result of treatment group with 0 patients in category.

b) Serious Adverse Events

Serious adverse events (SAEs) are any adverse events that:

- Result in death,
- Require or prolongs hospitalization,
- Result in serious injury or permanent impairment, or
- Require surgical intervention to prevent death or serious injury

Table 18 below lists all of the SAEs, showing 95 events in 68 patients (31.8%) and 86 events in 57 patients (30.0%) in the PCM and ACDF groups, respectively. SAEs reported at an incidence rate greater than 3% were: systemic musculoskeletal/back/leg pain (6.5%), systemic musculoskeletal/other (4.7%), systemic musculoskeletal/spinal event (4.7%), implant-related displacement/loosening (3.7%), systemic musculoskeletal/neck/arm pain (3.3%), and systemic other (3.3%) in the PCM group. For the ACDF group, these included systemic musculoskeletal/spinal event (5.8%), systemic other (5.8%), systemic musculoskeletal/neck/arm pain (4.2%), systemic musculoskeletal trauma (4.2%), and urogenital (3.2%).

Some of the reported SAEs include SSSIs that occurred at the index level as well as major complications. Please refer to ***Section c) Major Complications*** and ***Section d) Subsequent Secondary Surgical Interventions*** below for additional information.

Table 18: Serious Adverse Events
(Safety Population)

Adverse Event	PCM (N=214)		ACDF (N=190)	
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
Total Serious Adverse Events (SAEs)	**68 (31.8%)**	**95 (0.44)**	**57 (30.0%)**	**86 (0.45)**
Implant Related - Adjacent Level Disease	4 (1.9%)	4 (0.02)	4 (2.1%)	4 (0.02)
Implant Related - Implant Displacement/Loosening	8 (3.7%)	8 (0.04)	0 (0.0%)	0 (0.0)
Implant Related - Non-union	0 (0.0%)	0 (0.0)	2 (1.1%)	3 (0.02)
Implant Related - Spinal Event	3 (1.4%)	4 (0.02)	0 (0.0%)	0 (0.0)
Implant Related - Subsidence	1 (0.5%)	1 (<0.01)	0 (0.0%)	0 (0.0)
Implant Related - Trauma	1 (0.5%)	1 (<0.01)	1 (0.5%)	1 (0.01)
Surgery Related - Neck/Arm Pain	2 (0.9%)	2 (0.01)	4 (2.1%)	4 (0.02)
Surgery Related - Neurologic	2 (0.9%)	2 (0.01)	3 (1.6%)	3 (0.02)
Surgery Related - Spinal Event	0 (0.0%)	0 (0.0)	2 (1.1%)	2 (0.01)
Systemic - Cardiac Events	3 (1.4%)	3 (0.01)	3 (1.6%)	3 (0.02)
Systemic - Gastrointestinal	4 (1.9%)	5 (0.02)	2 (1.1%)	2 (0.01)
Systemic - Infection	5 (2.3%)	5 (0.02)	3 (1.6%)	4 (0.02)
Systemic - Mental Disorder	0 (0.0%)	0 (0.0)	3 (1.6%)	3 (0.02)
Systemic - Musculoskeletal Trauma	4 (1.9%)	4 (0.02)	8 (4.2%)	10 (0.05)
Systemic - Musculoskeletal/Adjacent Level Disease	1 (0.5%)	1 (<0.01)	0 (0.0%)	0 (0.0)
Systemic - Musculoskeletal/Back/Leg Pain	14 (6.5%)	18 (0.08)	5 (2.6%)	5 (0.03)
Systemic - Musculoskeletal/Neck/Arm Pain	7 (3.3%)	10 (0.05)	8 (4.2%)	9 (0.05)
Systemic - Musculoskeletal/Other	10 (4.7%)	10 (0.05)	2 (1.1%)	2 (0.01)
Systemic - Musculoskeletal/Spinal Event	10 (4.7%)	10 (0.05)	11 (5.8%)	11 (0.06)
Systemic - Neurologic	0 (0.0%)	0 (0.0)	2 (1.1%)	2 (0.01)
Systemic - Other	7 (3.3%)	7 (0.03)	11 (5.8%)	11 (0.06)
Systemic - Respiratory	0 (0.0%)	0 (0.0)	1 (0.5%)	1 (0.01)
Systemic - Urogenital	0 (0.0%)	0 (0.0)	6 (3.2%)	6 (0.03)

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

Table 19 below lists the SAEs for the PCM-V subgroup. At 24 months, the PCM Standard sub-group had 10 (7.5%) device related or procedure related SAEs versus 2 (2.5%) in the PCM-V sub-group.

Table 19: Serious Adverse Events (SAEs) to 24 Months by Sub-group
(Safety Population)

	PCM-V (N=81)	ACDF (N=190)
Any SAE	24 (29.6%)	41 (21.6%)
Device or Procedure-related SAE	2 (2.5%)	14 (7.4%)

The PCM-V cohort was not powered for statistical comparison with the control group; however, it was determined that the investigational sub-groups were poolable. The randomized investigational group (PCM Standard and PCM-V) was adequately powered for a non-inferiority comparison with the control group. The table above is provided for clinical interpretation.

c) Major Complications

Major complications, a component of the primary endpoint definition, were defined in the PCM Clinical Study Protocol as any of the following AEs that are related to the PCM or ACDF control device system or device component: documented permanent neurologic damage or permanent nerve root injury; vessel injury, bleeding, or hematoma requiring surgical intervention; deep infection requiring surgical intervention (irrigation / debridement) or intravenous antibiotics; spontaneous fusion of the treatment site (PCM patients only); or failure of fusion of the treated level (ACDF patients only), defined as ≥2° of segmental movement on lateral flexion/extension x-rays and radiolucent lines at >50% of the graft-vertebra interfaces.

Major complications are identified through adverse event reporting, radiological assessments (independent), and neurological exams. Major complications reported as adverse events included two ACDF patients experienced major complications (both patients were diagnosed with Reflex Sympathetic Dystrophy).

In addition, one death due to a recurrent prior cancer was reported in the study. This was unrelated to the surgery or device and therefore did not meet the criteria of a Major Complication. This patient was included in the MITT population, but excluded from the Per Protocol and Per Protocol In Window population.

Radiographic complications were composed of an assessment of fusion of the operative level. If a patient in the PCM group was observed to have fused at the operative level, then this would be considered a major complication. Conversely, in the ACDF group, a patient that was observed to have not fused would be considered a major complication. In the PCM group there were 1.1% (2/189) radiographic complications and 8.9% (14/157) radiographic complications in the ACDF group.

Neurological complications were defined as a decrease in muscle strength or muscle atrophy, progression of anaesthesia or paresthesia in a specific cervical distribution, or the new onset of pathological reflexes. Neurological complications were observed in 10% (6/60) of Training, 5.5% (11/199) of PCM, and 10.2% (16/157) of ACDF patients.

d) Subsequent Secondary Surgical Interventions

Subsequent Secondary Surgical Interventions (SSSIs) are defined as revisions, reoperations, supplemental fixations, and device removals that were performed at the original index level. SSSI events classified as *revisions* represent those events where a surgical procedure was performed at the index level, where the device was modified in position or construct, but was not removed. *Removals* indicate a surgical procedure has taken place at the index level where all of the original device system has been removed. *Supplemental fixations* include those surgical procedures at the index level where additional components or systems not under the study were added, and the original implant system remains. *Reoperations* include only those surgical procedures that occur at the index level, but do not include the adjustment, modification or removal of the implanted system (such as the drainage of a hematoma). Per the protocol, the occurrence of any of these events constituted a patient failure in the clinical study. In addition, these events were generally considered to be related to the surgical device.

The SSSI rates a 24 Months based on various analysis populations are presented in ***Table 20***. No significant difference in SSSI rates were observed between the groups.

Table 20: Subsequent Secondary Surgical Intervention at 24 Months

Analysis Population	Training	PCM	ACDF	P-Value*
Modified Intent-to-Treat (MITT)†	7/76 (9.2%)	12/218 (5.5%)	10/185 (5.4%)	1.000
Per Protocol‡	7/75 (9.3%)	11/211 (5.2%)	10/184 (5.4%)	1.000
Safety§	7/75 (9.3%)	11/214 (5.1%)	11/190 (5.4%)	0.828

Note: 1. Adverse Events (AEs) based on cumulative AE database as of September 2011.
2. SSSI (Subsequent Secondary Surgical Intervention) includes revisions, reoperations, removals, and supplemental fixation, although only reoperations and removals were observed.

* Comparing PCM and ACDF (two-sided Fisher's exact test).
† Includes any patient who received treatment (analyzed by group the patient was enrolled/randomized to).
‡ Includes any patients who received the treatment they were randomized to and adhered to the protocol.
§ Includes any patients who received treatment (analyzed by the treatment they actually received). One Training and 4 PCM patients were switched to ACDF during surgery.
P-values are not adjusted for multiplicity. They are included to help clinical interpretation, without defining statistical significance.

As shown in ***Table 21***, there were 11 SSSI events in the Training group, 16 in the PCM group, and 14 in the ACDF group.

Table 21: Secondary Surgical Interventions at the Index Level (Safety Population)

	Intraop (0 - 2 Days)			Periop (>2 Days - 6 Wks.)			Short Term (>6 Wks. - 12 Mon.)			Long Term (>12 - 24 Mon.)			Longer Term (>24 Mon.)			Patients (%)		
	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN (N=75)	PCM (N=214)	ACDF (N=190)
Revision	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0%)	0 (0%)	0 (0%)
Removal	0	0	0	1	0	1	2	6	1	2†	2	5	4	5	7	9 (12.0%)	13 (6.1%)	14 (7.4%)
Reoperation	0	0	0	0	0	0	2	1	0	0	2	0	0	0	0	2 (2.7%)	3 (1.4%)	0 (0%)
Supplemental Fixation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0%)	0 (0%)	0 (0%)
Total (Patients)	0	0	0	1	0	1	4	7	1	2†	4	5	4	5	7	9 (12.0%)	16 (7.5%)	14 (7.4%)
Total (Events)	0	0	0	1	0	1	4	7	1	2	4	5	4	5	7	11	16	14

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

† The two Training (TRN) patients who had reoperations during the Short Term period had removals during the Long Term period.

There were 27 secondary surgical procedures performed in the Training and PCM groups. There were 22 device removals (4 with two-level fusions), 4 foraminotomy procedures, and 1 laminoplasty procedure. For the device removal procedures, 13 were removed for pain adverse events (5 for pain alone, 6 for pain associated with device migration, loosening, or subsidence, and 2 for adjacent level disease), 5 for dysphagia associated with migration adverse events, 2 for migration alone, and 2 for unknown causes. The foraminotomy procedures were performed for neck and/or arm pain or adjacent level disease. The laminoplasty procedure was performed for unresolved pain and multi-level spinal stenosis. Two removals for dysphagia occurred early (42 and 44 days postoperatively), and 3 were performed at later time points (202, 1,134, and 1,486 days postoperatively). Within the randomized investigational cohort at 24 months extended window, 3 (3.8%) PCM-V patients, 8 (6.1%) PCM Standard patients experienced a Subsequent Secondary Surgical Intervention.

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Table 22 below lists the Secondary Surgical Procedure Details for the All PCM group (Training and PCM).

Table 22: Secondary Surgical Procedure Details (Safety Population)

Group	Level	Cause/Adverse Event	Action	Days
PCM Training Group				
TRN	C6-7	Dysphagia, device migration	Removal with ACDF	42
TRN	C5-6	Unresolved pain followed by trauma	Removal with ACDF	152
TRN	C5-6	Dysphagia, device migration	Removal with ACDF	202
TRN	C6-7	Arm and Shoulder Pain	Posterior Foraminotomy	245
TRN	C5-6	Pain/Radiculopathy due to osteophytes	C6 Left Foraminotomy	364
TRN	C6-7	Increased pain, adjacent segment disease, implant loosening	Removal with 2 level ACDF (C5-6)	569
TRN	C5-6	Unresolved pain	Removal with ACDF	696
TRN	C5-6	Trauma followed by pain and migration	Removal with ACDF	801
TRN	C6-7	Unresolved pain, device migration	Removal with ACDF	981
TRN	C6-7	Increased arm pain, adjacent disease	Removal with 2 level fusion (C7-T1), osteophytectomy (C4-5)	876
TRN	C6-7	Unknown	Removal	1092
PCM Investigational Group				
PCM	C6-7	Dysphagia, device migration	Removal with ACDF	44
PCM	C5-6	Migration	Removal with ACDF	56
PCM	C4-5	Neck pain and subsidence	Removal with ACDF	137
PCM	C4-5	Unresolved pain, multi-level stenosis	C3-7 Laminoplasty	147
PCM	C5-6	Neck and shoulder pain	Removal with ACDF	181
PCM	C5-6	Pain, adjacent segment disease, trauma and device migration	Removal with ACDF	225
PCM	C5-6	Increased neck and arm pain	Removal with ACDF	328
PCM	C5-6	Increased neck pain, multi-level stenosis	2 Level Bilateral Neuroforaminotomy & Hemilaminotomy (C6-7)	410
PCM	C6-7	Increased neck pain, adjacent level pseudoarthrosis	2 level Removal with ACDF and Foraminotomy (C5-6)	581
PCM	C5-6	Unknown	Removal	631
PCM	C4-5	Increased neck pain, adjacent disease	Foraminotomy, adjacent TDR (C3-4)	640
PCM	C5-6	Trauma followed by pain and adjacent disease	Removal with 2 level ACDF (C4-5)	938
PCM	C5-6	Trauma followed by pain and migration	Removal with ACDF	1083
PCM	C6-7	Trauma followed by migration and dysphagia	Removal and implant of Prodisc	1134
PCM	C6-7	Device migration	Removal with ACDF	1281
PCM	C5-6	Dysphagia, migration	Removal with ACDF	1486

Note: Adverse Events (AEs) based on cumulative AE database as of September 2011.

e) Unanticipated Adverse Device Effects (UADEs)

There were no UADEs identified over the course of the study as determined by the Clinical Events Committee. However, during the course of the study the FDA believed one AE was a UADE because it resulted from the ACDF treatment of a patient at the incorrect level.

f) Neurological Assessment

Neurological evaluations that consisted of motor strength, sensory, and reflex, were routinely performed as a part of the study's safety assessments. ***Table 23*** presents a summary of neurological status. Patient neurological status was compared to their preoperative status at the 3 Months, 6 Months, 12 Months, and 24 Months, postoperative time points and categorized as neurologically stable or improved. At 24 Months, 90.7% of the patients in the Training group, 94.7% of the patients in the PCM group were determined to be neurological stable or improved compared to 89.5% of the patients in the ACDF group.

Table 23: Neurological Status
(Per Protocol In Window Population)

Month	Status	Training	PCM	ACDF
3	Stable or Improved	47/52 (90.4%)	171/182 (94.0%)	135/150 (90.0%)
6	Stable or Improved	45/52 (86.5%)	175/184 (95.1%)	134/146 (91.8%)
12	Stable or Improved	50/53 (94.3%)	174/185 (94.1%)	131/147 (89.1%)
24	Stable or Improved	49/54 (90.7%)	178/188 (94.7%)	137/153 (89.5%)

2) Effectiveness Results

The analysis of effectiveness was based on the Per Protocol population comprised of 470 total patients (75 Training, 211 PCM, and 184 ACDF). Of these patients, 396 patients were evaluable on the primary endpoint (56 Training patients, 189 PCM patients, and 151 ACDF patients).

a) Primary Endpoint - Overall Success

The primary overall success endpoint is a composite of several subcomponents, each of which must be a success in order for a patient to be deemed an overall success. The primary overall success was evaluated at 24 Months postoperative based on the Per Protocol population. The primary overall success endpoint comparison was made between the PCM and the ACDF treatment groups.

A patient experiencing a safety device failure (i.e., SSSI) within 30 months of surgery was classified as a failure on the overall success endpoint regardless of the other subcomponent determinations or lack thereof. In addition, if a patient had missing subcomponent results, but were a known failure on any other subcomponent; the patient was classified as a failure on the overall success endpoint. Finally, if a patient's overall success endpoint could not be adequately determined due to missing or insufficient data, the primary endpoint was considered missing and the patient was excluded from the primary endpoint analysis.

Table 24 presents the primary endpoint as subcomponent success at 24 Months based on the Per Protocol population. The PCM group had an overall success rate of 75.1% (142/189)

compared to 64.9% (98/151) ACDF group. The corresponding 90% confidence interval for the difference in success rates is 2.0% to 18.5%. Therefore, based on the FDA-requested non-inferiority delta of 10.0%, non-inferiority was demonstrated ($p < 0.0001$).

Table 24: Primary Endpoint and Subcomponent Success at 24 Months (Per Protocol Population with a Primary Endpoint)

Component	Training (N=56)	PCM (N=189)	ACDF (N=151)
NDI (≥20% Improvement)	45/54 (83.3%) [71.0% - 91.2%]	154/186 (82.8%) [76.7% - 87.6%]	121/149 (81.2%) [74.1% - 86.7%]
Neurological Success	48/53 (90.6%) [79.3% - 96.3%]	177/187 (94.7%) [90.3% - 97.2%]	134/150 (89.3%) [83.3% - 93.4%]
SSSI Success[§]	49/56 (87.5%) [76.1% - 94.1%]	178/189 (94.2%) [89.8% - 96.8%]	141/151 (93.4%) [88.1% - 96.5%]
Radiographic Success	50/51 (98.0%) [88.7% - 100.0%]	178/180 (98.9%) [95.8% - 100.0%]	138/150 (92.0%) [86.4% - 95.5%]
Overall Success	38/56 (67.9%) [54.8% - 78.6%]	142/189 (75.1%) [68.5% - 80.8%]	98/151 (64.9%) [57.0% - 72.1%]

§ Absence of SSSI (Subsequent Secondary Surgical Intervention) includes revisions, reoperations, removals, and supplemental fixation, although only reoperations and removals were observed.

Confidence intervals provided under the rates were determined using the Adjusted Wald by Agresti-Coull method.

In addition to the protocol-defined overall success criteria, FDA established an alternate definition of overall success to include improvement in NDI of ≥15-points rather than ≥20% from baseline. Analysis using the alternate-defined endpoint is provided in ***Table 25***. As shown in ***Table 25***, the PCM group had an overall success rate of 72.0% (136/189) compared to 60.9% (92/151) in the ACDF group. The corresponding 90% confidence interval for the difference in success rates is 2.6% to 19.5%. Therefore, based on the FDA-requested non-inferiority delta of 10.0%, non-inferiority was demonstrated ($p < 0.0001$). .

Table 25: Alternate Primary Endpoint and Subcomponent Success at 24 Months (Per Protocol Population with a Primary Endpoint)

Component	Training (N=56)	PCM (N=189)	ACDF (N=151)
NDI (≥15-Point Improvement)	42/54 (77.8%) [64.9% - 87.0%]	147/186 (79.0%) [72.6% - 84.3%]	112/149 (75.2%) [67.6% - 81.4%]
Neurological Success	48/53 (90.6%) [79.3% - 96.3%]	177/187 (94.7%) [90.3% - 97.2%]	134/150 (89.3%) [83.3% - 93.4%]
SSSI Success§	49/56 (87.5%) [76.1% - 94.1%]	178/189 (94.2%) [89.8% - 96.8%]	141/151 (93.4%) [88.1% - 96.5%]
Radiographic Success	50/51 (98.0%) [88.7% - 100.0%]	178/180 (98.9%) [95.8% - 100.0%]	138/150 (92.0%) [86.4% - 95.5%]
Overall Success	37/56 (66.1%) [53.0% - 77.1%]	136/189 (72.0%) [65.1% - 77.9%]	92/151 (60.9%) [53.0% - 68.3%]

§ Absence of SSSI (Subsequent Secondary Surgical Intervention) includes revisions, reoperations, removals, and supplemental fixation, although only reoperations and removals were observed.
Confidence intervals provided under the rates were determined using the Adjusted Wald by Agresti-Coull method.

Table 26 presents the PCM-V primary endpoint as subcomponent success at 24 Months based on the Per Protocol population.

Table 26: Primary Endpoint and Subcomponent Success by Subgroup at 24 Months (Per Protocol Population with a Primary Endpoint)

Component	PCM-V (N=73)	ACDF (N=151)
NDI (≥20% Improvement)	63/73 (86.3%) [76.4% - 92.6%]	121/149 (81.2%) [74.1% - 86.7%]
Neurological Success	72/73 (98.6%) [91.9% - 100.0%]	134/150 (89.3%) [83.3% - 93.4%]
SSSI Success§	70/73 (95.9%) [88.1% - 99.1%]	141/151 (93.4%) [88.1% - 96.5%]
Radiographic Success	70/70 (100.0%) [93.8% - 100.0%]	138/150 (92.0%) [86.4% - 95.5%]
Overall Success	60/73 (82.2%) [71.7% - 89.4%]	98/151 (64.9%) [57.0% - 72.1%]

§ Absence of SSSI (Subsequent Secondary Surgical Intervention) includes revisions, reoperations, removals, and supplemental fixation, although only reoperations and removals were observed.
Confidence intervals provided under the rates were determined using the Adjusted Wald by Agresti-Coull method.

The PCM-V sub-group had an overall success rate of 82.2% (60/73), while the PCM Standard sub-group had an overall success rate of 70.7% (82/116). The PCM-V cohort was not powered for statistical comparison with the control group; however, it was determined that the investigational sub-groups were poolable. The randomized investigational group (PCM Standard and PCM-V) was adequately powered for a non-inferiority comparison with the control group. The table above is provided for clinical interpretation.

The rates of protocol-defined overall success at 6 Months, 12 Months, 24 Months, 36 Months, and 48 Months for the Training, PCM, and ACDF groups are presented in ***Table 27***. For the PCM group, the Overall Success rates ranged from 72.5% to 83.5%. For the ACDF group, the Overall Success rates ranged from 33.1% to 64.9%. Using the FDA alternate-defined overall success, the overall success rates for the PCM group ranged from 71.1% to 73.2%, and for the ACDF group ranged from 61.7% to 73.5%.

Table 27: Time Course of Primary Overall Success Endpoint (Per Protocol Population)

Overall Success	Group	Months				
		6	12	24	36	48*
Protocol Definition (NDI; ≥20% Improvement)	TRN (N=75)	48/67 (71.6%)	47/65 (72.3%)	38/56 (67.9%)	34/51 (66.7%)	28/46 (60.9%)
	PCM (N=211)	167/200 (83.5%)	155/198 (78.3%)	142/189 (75.1%)	132/182 (72.5%)	114/155 (73.5%)
	ACDF (N=184)	54/163 (33.1%)	84/156 (53.8%)	98/151 (64.9%)	85/136 (62.5%)	71/117 (60.7%)
Alternate Definition (NDI; ≥15-Point Improvement)	TRN (N=75)	47/67 (70.1%)	46/65 (70.8%)	37/56 (66.1%)	33/51 (64.7%)	28/46 (60.9%)
	PCM (N=211)	157/200 (78.5%)	146/198 (73.7%)	136/189 (72.0%)	128/182 (70.3%)	109/155 (70.3%)
	ACDF (N=184)	51/163 (31.3%)	82/156 (52.6%)	92/151 (60.9%)	80/136 (58.8%)	67/117 (57.3%)

* Not all patients completed 48 Months follow-up as of September 2011.

The overall success rates by treatment level are provided in ***Table 28***.

Table 28: Primary Overall Success Endpoint at 24 Months by Level Treated (Per Protocol Population with a Primary Endpoint)

Overall Success	Training (N=56)	PCM (N=189)	ACDF (N=151)
Protocol Definition (NDI; ≥20% Improvement)			
C3-4	1/1 (100.0%) [16.8% - 100.0%]	0/0 (0.0%) [NA]	4/6 (66.7%) [29.6% - 90.8%]
C4-5	2/3 (66.7%) [20.2% - 94.4%]	23/30 (76.7%) [58.8% - 88.5%]	8/11 (72.7%) [42.9% - 90.8%]
C5-6	19/27 (70.4%) [51.3% - 84.3%]	67/95 (70.5%) [60.7% - 78.8%]	51/81 (63.0%) [52.1% - 72.7%]
C6-7	16/24 (66.7%) [46.6% - 82.2%]	51/62 (82.2%) [70.8% - 90.0%]	35/53 (66.0%) [52.5% - 77.4%]
C7-T1	0/1 (0.0%) [0.0% - 83.2%]	1/2 (50.0%) [9.4% - 90.5%]	0/0 [NA]
Alternate Definition (NDI; ≥15-Point Improvement)			
C3-C4	1/1 (100.0%) [16.8% - 100.0%]	0/0 (0.0%) [NA]	4/6 (66.7%) [29.6% - 90.8%]
C4-C5	2/3 (66.7%) [20.2% - 94.4%]	21/30 (70%) [52.0% - 83.5%]	8/11 (72.7%) [42.9% - 90.8%]
C5-C6	19/27 (70.4%) [51.3% - 84.3%]	65/95 (68.4%) [58.5% - 76.9%]	48/81 (59.3%) [48.4% - 69.3%]
C6-C7	15/24 (62.5%) [42.6% - 78.9%]	49/62 (79.0%) [67.2% - 87.5%]	32/53 (60.4%) [46.9% - 72.4%]
C7-T1	0/1 (0.0%) [0.0% - 83.2%]	1/2 (50.0%) [9.4% - 90.5%]	0/0 (0.0%) [NA]

Confidence intervals provided under the rates were determined using the Adjusted Wald by Agresti-Coull method.

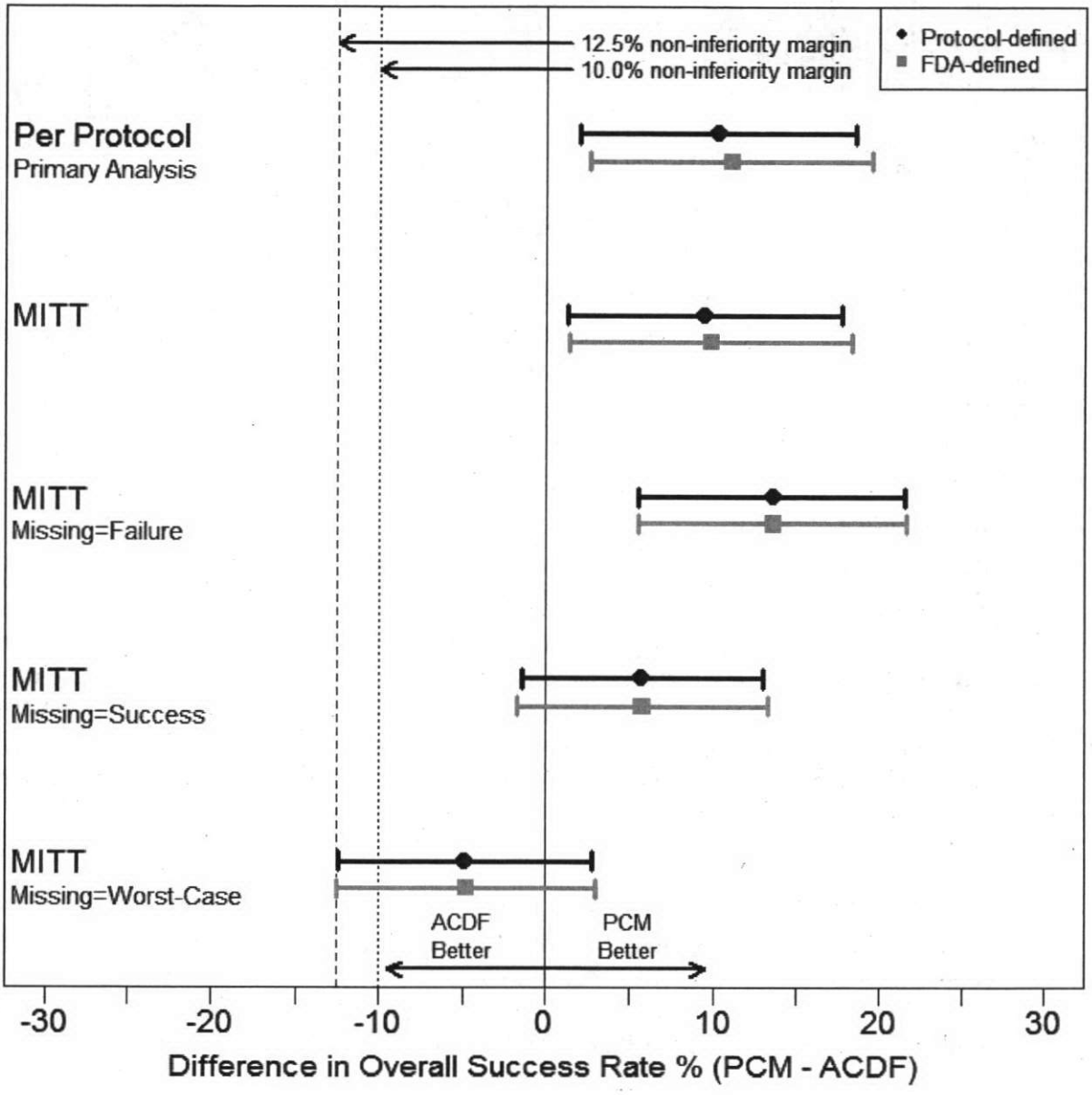
b) Sensitivity and Subgroup Analyses

Various sensitivity analyses were conducted to assess the impact of missing data and the robustness of the study conclusions with regards to the primary overall success endpoint. In the sensitivity analysis scenarios, patients in the MITT (treated) population with a missing primary overall success endpoint were imputed as follows:

- Missing=Failure: All missing primary endpoint are considered failures;
- Missing=Success: All missing primary endpoint was considered successes;
- Missing=Worst-Case: All missing PCM patients' primary endpoint are considered failures, while all missing ACDF patients' primary endpoint are considered successes.

Figure 3 illustrates the 90% confidence interval for the difference in overall success between PCM and ACDF groups using the both the protocol-defined and FDA alternative-defined primary endpoint under various analysis scenarios. Non-inferiority is demonstrated if the entire 90% confidence interval lies entirely to the right of -10.0%. Using both the protocol-defined and FDA alternative-defined primary overall success endpoint, non-inferiority was demonstrated for all scenarios with the exception of the Worst-Case scenario using the FDA alternative-defined primary endpoint.

Figure 3: 90% Confidence Intervals for the Difference in Overall Success (Protocol-Defined and FDA Alternate-Defined Overall Success)



i. Prior Fusion

Table 29 presents the protocol-defined primary overall success stratified by prior fusion. In patients with prior fusion, overall success for the protocol-defined primary endpoint was met in 65.4% (17/26) of PCM and 64.3% (9/14) of ACDF patients. In patients without prior fusions, 76.7% (125/163) of PCM and 65% (89/137) of ACDF groups met overall success. Results for the FDA alternate-definition are similar.

Table 29: Primary Overall Success Endpoint at 24 Months by Prior Fusion (Per Protocol Population with a Primary Endpoint)

Overall Success	PCM (N=189)		ACDF (N=151)	
	No Prior Fusion	Prior Fusion	No Prior Fusion	Prior Fusion
Protocol Definition (NDI; ≥20% Improvement)	125/163 (76.7%) [69.6% - 82.5%]	17/26 (65.4%) [46.1% - 80.7%]	89/137 (65.0%) [56.7% - 72.5%]	9/14 (64.3%) [38.6% - 83.8%]
Alternate Definition (NDI; ≥15-Point Improvement)	119/163 (73.0%) [65.7% - 79.2%]	17/26 (65.4%) [46.1% - 80.7%]	84/137 (61.3%) [52.9% - 69.1%]	8/14 (57.1%) [32.6% - 78.7%]

Confidence intervals provided under the rates were determined using the Adjusted Wald by Agresti-Coull method.

ii. Financial Disclosure Analysis

Analyses were performed to determine if there was any relationship between the financial interest of the investigators/sites and the primary overall success endpoint (both protocol-specified and FDA alternate-defined) at 24 Months. No significant relationships between success rates and financial interest were observed.

iii. Poolability Analysis

Poolability of the primary overall success endpoint results across investigational sites was confirmed using the Breslow-Day test of homogeneity of odds ratio (p=0.49).

A subgroup analysis was performed to confirm that the clinical and radiographic data between the PCM-Standard and PCM-V groups are poolable, as shown in the primary effectiveness and safety sections above. These analyses demonstrated that the PCM-Standard and PCM-V device configurations performed in a comparable manner to the ACDF. The rate of serious adverse events in the PCM-V and PCM Standard cohorts were comparable to ACDF. In PMA P100012, the applicant is only seeking marketing approval for the PCM-V.

c) Secondary Effectiveness Analyses

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed and the results are provided below.

Secondary effectiveness outcomes are summarized in table ***Table 30***.

Table 30: Secondary Effectiveness Endpoints at 24 Months (Per Protocol 24 Months In Window Population)

Component	PCM (N=189)	ACDF (N=153)
Clinical Endpoints		
Neck Disability Index (≥20% Improvement)	156/187 (83.4%)	123/151 (81.5%)
Neck Disability Index (≥15-Point Improvement)	149/187 (79.7%)	114/151 (75.5%)
VAS Neck Pain (≥20mm Improvement)	139/187 (74.3%)	113/150 (75.3%)
VAS Left Arm Pain (≥20mm Improvement)	107/187 (57.2%)	79/150 (52.7%)
VAS Right Arm Pain (≥20mm Improvement)	89/187 (47.6%)	80/150 (53.3%)
VAS Worst Arm Pain (≥20mm Improvement)	148/187 (79.1%)	113/150 (75.3%)
SF-36 PCS (≥15% Improvement)	133/187 (71.1%)	98/151 (64.9%)
SF-36 MCS (≥15% Improvement)	87/187 (46.5%)	75/151 (49.7%)
Myelopathy (Nuricks: Maintained or Improved)	185/185 (100.0%)	148/153 (96.7%)
Dysphagia Bazaz Score (Maintained or Improved)	164/187 (87.7%)	123/149 (82.6%)
Dysphagia VAS Hoarseness, mean (SD) mm	7.3 (14.3)	10.1 (18.5)
Dysphagia VAS Swallowing, mean (SD) mm	8.8 (16.3)	12.1 (20.1)
Patient Satisfaction VAS, mean (SD) mm	82.8 (27.1)	81.4 (25.7)
Satisfaction (Odom's Criteria)		
Excellent	129/188 (68.6%)	82/153 (53.6%)
Good	43/188 (22.9%)	50/153 (32.7%)
Fair	15/188 (8.0%)	15/153 (9.8%)
Poor	1/188 (0.5%)	6/153 (3.9%)
Radiographic Endpoints		
Range of Motion, mean (SD) degrees	5.7 (3.9)	0.8 (0.8)
Hypermobility†	179/181 (98.9%)	149/149 (100.0%)
Normal Disc Height (≥80% of Superior Level)	176/182 (96.7%)	119/140 (85.0%)
Disc Height Maintenance (≥80% of Postoperative)	160/177 (90.4%)	112/135 (83.0%)
Radiolucency (>50% Length of the Prosthesis or Graft)		
Superior Level	14/182 (7.7%)	0/152 (0.0%)
Inferior Level	0/182 (0.0%)	0/152 (0.0%)
Dynamic Canal Stenosis‡	1/182 (0.5%)	4/144 (2.8%)
Adjacent Level Degeneration§		
Superior	30/175 (17.1%)	35/137 (25.6%)
Inferior	34/147 (23.1%)	35/119 (29.4%)
Either level	59/151 (39.1%)	60/122 (49.2%)

† Reitman *et al.*, *Spine*, 2004.[10]
‡ Baba *et al.*, *Spine*, 1993.[11]
§ Walraevens *et al.*, *European Spine Journal*, 2009.[12]

i. Neck Disability Index

Table 31 presents the time course of success for NDI improvement, both for ≥20% and ≥15-Point Improvement. Both randomized groups demonstrated similar improvement in NDI.

Table 31: Time Course of Neck Disability Index Improvement (Per Protocol 24 Months In Window Population)

	6 Weeks			3 Months			6 Months			12 Months			24 Months		
	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)
Significant Improvement (≥15-Points)	41/54 (75.9%)	135/186 (72.6%)	86/145 (59.3%)	43/53 (81.1%)	149/180 (82.8%)	109/148 (73.6%)	43/52 (82.7%)	153/184 (83.2%)	115/139 (82.7%)	46/53 (86.8%)	150/186 (80.6%)	116/146 (79.5%)	43/55 (78.2%)	149/187 (79.7%)	114/151 (75.5%)
Some Improvement (≥0-Points, <15-Points)	10/54 (18.5%)	37/186 (19.9%)	46/145 (31.7%)	7/53 (13.2%)	28/180 (15.6%)	28/148 (18.9%)	3/52 (5.8%)	25/184 (13.6%)	16/139 (11.5%)	1/53 (1.9%)	28/186 (15.1%)	23/146 (15.8%)	7/55 (12.7%)	27/187 (14.4%)	22/151 (14.6%)
Deterioration (<0-Points)	3/54 (5.6%)	14/186 (7.5%)	13/145 (9.0%)	3/53 (5.7%)	3/180 (1.7%)	11/148 (7.4%)	6/52 (11.5%)	6/184 (3.3%)	8/139 (5.8%)	6/53 (11.3%)	8/186 (4.3%)	7/146 (4.8%)	5/55 (9.1%)	11/187 (5.9%)	15/151 (9.9%)
Significant Improvement (≥20%)	47/54 (87.0%)	144/186 (77.4%)	104/145 (71.7%)	49/53 (92.5%)	155/180 (86.1%)	116/148 (78.4%)	45/52 (86.5%)	162/184 (88.0%)	118/139 (84.9%)	47/53 (88.7%)	159/186 (85.5%)	119/146 (81.5%)	46/55 (83.6%)	156/187 (83.4%)	123/151 (81.5%)
Some Improvement (≥0%, <20%)	4/54 (7.4%)	28/186 (15.1%)	28/145 (19.3%)	1/53 (1.9%)	22/180 (12.2%)	21/148 (14.2%)	1/52 (1.9%)	16/184 (8.7%)	13/139 (9.4%)	0/53 (0.0%)	19/186 (10.2%)	20/146 (13.7%)	4/55 (7.3%)	20/187 (10.7%)	13/151 (8.6%)
Deterioration (<0%)	3/54 (5.6%)	14/186 (7.5%)	13/145 (9.0%)	3/53 (5.7%)	3/180 (1.7%)	11/148 (7.4%)	6/52 (11.5%)	6/184 (3.3%)	8/139 (5.8%)	6/53 (11.3%)	8/186 (4.3%)	7/146 (4.8%)	5/55 (9.1%)	11/187 (5.9%)	15/151 (9.9%)

ii. VAS Neck and Arm Pain

The time course of VAS neck and arm pain scores and Month 24 improvement are presented in ***Table 32*** and ***Table 33***, respectively. Both randomized groups demonstrated similar improvement in VAS neck and worst arm pain.

Table 32: Time Course of VAS Neck and Arm Pain (Per Protocol 24 Months In Window Population)

	Preoperative			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)
n (Observed)	55	187	150	54	186	145	53	179	147	52	184	140	53	185	144	55	187	150
Neck, mean (SD) mm	66.8 (24.5)	68.4 (22.3)	73.5 (18.6)	24.6 (22.0)	28.2 (24.7)	31.7 (24.6)	23.1 (22.0)	24.4 (24.0)	26.5 (23.0)	22.8 (24.3)	25.0 (25.9)	26.5 (23.1)	19.9 (25.5)	23.4 (25.5)	31.6 (26.4)	23.4 (27.7)	26.1 (28.7)	30.4 (28.3)
Left Arm, mean (SD) mm	43.0 (36.7)	51.2 (33.9)	50.0 (32.6)	14.8 (19.6)	20.0 (24.4)	19.6 (24.5)	14.8 (21.1)	18.0 (23.7)	19.0 (25.0)	14.3 (20.7)	18.3 (23.9)	18.2 (23.8)	11.6 (19.4)	17.9 (23.7)	20.4 (24.7)	14.2 (21.5)	20.5 (26.5)	23.1 (25.7)
Right Arm, mean (SD) mm	49.3 (34.3)	47.9 (33.7)	50.6 (33.4)	13.5 (21.3)	23.0 (28.1)	21.8 (25.8)	16.4 (23.7)	20.8 (26.2)	21.5 (24.4)	13.9 (22.4)	20.0 (25.9)	21.8 (25.6)	15.6 (25.4)	20.0 (26.5)	22.7 (27.4)	15.9 (21.8)	22.4 (28.8)	24.9 (28.5)
Worst Arm*, mean (SD) mm	74.9 (17.3)	73.4 (19.4)	74.4 (18.2)	19.2 (23.1)	24.9 (27.2)	23.8 (26.9)	18.4 (25.5)	22.5 (25.7)	25.3 (27.0)	18.9 (25.4)	22.9 (26.7)	22.9 (25.4)	16.2 (23.9)	22.6 (27.2)	26.8 (28.9)	20.6 (25.9)	24.9 (29.2)	27.5 (28.3)

* Worst Arm defined at the arm with the highest preoperative VAS pain score. In the event of equal right and left preoperative VAS scores, the arm with the least 24 Months improvement.

Table 33: VAS Neck and Arm Changes from Baseline to 24 Months (Per Protocol 24 Months In Window Population)

	Training (N=56)	PCM (N=189)	ACDF (N=153)
n (Observed)	55	187	150
Neck			
Significant Improvement (≥20 mm)	41 (74.5%)	139 (74.3%)	113 (75.3%)
Some Improvement (≥3 mm, <20 mm)	8 (14.5%)	27 (14.4%)	18 (12.0%)
No Change (>-3 mm, <3 mm)	4 (7.3%)	11 (5.9%)	10 (6.7%)
Deterioration (≤–3 mm)	2 (3.6%)	10 (5.3%)	9 (6.0%)
Left Arm			
Significant Improvement (≥20 mm)	25 (45.5%)	107 (57.2%)	79 (52.7%)
Some Improvement (≥3 mm, <20 mm)	12 (21.8%)	23 (12.3%)	30 (20.0%)
No Change (>-3 mm, <3 mm)	13 (23.6%)	28 (15.0%)	12 (8.0%)
Deterioration (≤–3 mm)	5 (9.1%)	29 (15.5%)	29 (19.3%)
Right Arm			
Significant Improvement (≥20 mm)	35 (63.6%)	89 (47.6%)	80 (53.3%)
Some Improvement (≥3 mm, <20 mm)	6 (10.9%)	39 (20.9%)	14 (9.3%)
No Change (>-3 mm, <3 mm)	8 (14.5%)	28 (15.0%)	22 (14.7%)
Deterioration (≤–3 mm)	6 (10.9%)	31 (16.6%)	34 (22.7%)
Worst Arm*			
Significant Improvement (≥20 mm)	47 (85.5%)	148 (79.1%)	113 (75.3%)
Some Improvement (≥3 mm, <20 mm)	5 (9.1%)	18 (9.6%)	19 (12.7%)
No Change (>-3 mm, <3 mm)	1 (1.8%)	8 (4.3%)	6 (4.0%)
Deterioration (≤–3 mm)	2 (3.6%)	13 (7.0%)	12 (8.0%)

* Worst Arm defined at the arm with the highest preoperative VAS pain score. In the event of equal right and left preoperative VAS scores, the arm with the least 24 Months improvement.

iii. SF-36

The time course of SF-36 Physical Component Score (PCS) and Mental Component Score (MCS) scores and 24 Months improvement are presented in ***Table 34*** and ***Table 35***, respectively. Both randomized groups demonstrated similar improvement in SF-36 scores.

Table 34: Time Course of SF-36 Physical/Mental Component Scores (Per Protocol 24 Months In Window Population)

	Preoperative			6 Weeks			3 Months			6 Months			12 Months			24 Months		
	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)
n (Observed)	54	187	151	53	186	145	54	186	151	51	183	140	52	185	145	54	187	151
PCS, mean (SD)	36.3 (6.3)	34.4 (6.8)	34.6 (6.3)	43.8 (9.0)	41.6 (9.1)	39.8 (9.0)	47.6 (9.4)	45.4 (9.9)	44.0 (9.9)	48.6 (9.3)	47.1 (10.6)	45.7 (10.1)	49.4 (9.6)	46.3 (11.0)	45.0 (10.3)	48.4 (9.6)	46.6 (11.0)	45.0 (10.6)
MCS, mean (SD)	43.0 (12.7)	43.3 (12.3)	41.9 (11.4)	51.9 (9.1)	50.1 (11.5)	48.4 (11.9)	50.7 (11.0)	51.6 (9.8)	48.6 (12.0)	50.8 (11.5)	51.3 (10.2)	50.9 (10.4)	52.0 (10.4)	50.8 (11.1)	51.1 (10.4)	50.0 (12.1)	50.3 (11.1)	49.3 (11.4)

PCS = Physical Component Score; MCS = Mental Component Score.

Table 35: SF-36 Physical and Mental Component Score Changes from Baseline to 24 Months (Per Protocol 24 Months In Window Population)

	Training (N=56)	PCM (N=189)	ACDF (N=153)
n (Observed)	54	187	151
Physical Component Score (PCS)			
Significant Improvement (≥15)	23 (42.6%)	80 (42.8%)	62 (41.1%)
Some Improvement (≥2 points, <15)	23 (42.6%)	71 (38.0%)	48 (31.8%)
No Change (>-2, <2)	4 (7.4%)	17 (9.1%)	17 (11.3%)
Deterioration (≤–2)	4 (7.4%)	19 (10.2%)	24 (15.9%)
Mental Component Score (MCS)			
Significant Improvement (≥15)	14 (25.9%)	51 (27.3%)	42 (27.8%)
Some Improvement (≥2 points, <15)	18 (33.3%)	65 (34.8%)	57 (37.7%)
No Change (>-2, <2)	7 (13.0%)	29 (15.5%)	21 (13.9%)
Deterioration (≤–2)	15 (27.8%)	42 (22.5%)	31 (20.5%)

iv. Patient Satisfaction

Patient Satisfaction, measured on a 0-100 VAS scale, for 12 and 24 Months are presented in ***Table 36*** for the Per Protocol population. At 12 Months, the PCM group had a mean of 86.0 mm compared to 78.2 mm. At 24 Months, the PCM group had a mean of 82.8 mm compared to 81.4 mm.

Table 36: Patient Satisfaction VAS
(Per Protocol 24 Months In Window Population)

	12 Months			24 Months		
	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)
n (Observed)	45	178	139	53	182	146
Mean (SD) mm	87.0 (23.2)	86.0 (23.0)	78.2 (26.8)	85.7 (24.7)	82.8 (27.1)	81.4 (25.7)

v. Satisfaction Index (Odom's Criteria)

Patient outcomes are also assessed by the Satisfaction Index (Odom's criteria), which is more accurately described as the investigator's perception of the patient's outcome. Odom's Criteria is a four-point scale ranging from a score of 1 for a perceived poor result to a score of 4 for a perceived excellent result. ***Table 37*** provides a summary of Satisfaction Index (Odom's Criteria) at 12 and 24 Months postoperative.

Table 37: Satisfaction Index (Odom's Criteria)
(Per Protocol 24 Months In Window Population)

Month	Group	Poor (1)	Fair (2)	Good (3)	Excellent (4)
12	TRN (N=56)	3/54 (5.6%)	4/54 (7.4%)	12/54 (22.2%)	35/54 (64.8%)
	PCM (N=189)	1/185 (0.5%)	10/185 (5.4%)	43/185 (23.2%)	131/185 (70.8%)
	ACDF (N=153)	1/148 (0.7%)	15/148 (10.1%)	53/148 (35.8%)	79/148 (53.4%)
24	TRN (N=56)	1/55 (1.8%)	2/55 (3.6%)	16/55 (29.1%)	36/55 (65.5%)
	PCM (N=189)	1/188 (0.5%)	15/188 (8.0%)	43/188 (22.9%)	129/188 (68.6%)
	ACDF (N=153)	6/153 (3.9%)	15/153 (9.8%)	50/153 (32.7%)	82/153 (53.6%)

Patient Satisfaction success was defined as a response of Excellent (score=4). At 12 Months, the PCM group reported 70.8% (131/185) Excellent results compared to the 53.4% (79/148) Excellent results in the ACDF group. At 24 Months, Excellent results were reported by 68.6% (129/188) and 53.6% (82/153) for the PCM and the ACDF group, respectively.

vi. Dysphagia

Dysphagia was evaluated for hoarseness and swallowing difficulty on a 100-point VAS scale. For this measurement, a lower score indicates the patient is experiencing less difficulty swallowing. No baseline measurement was taken, but an evaluation was performed at every postoperative time point. As reported in ***Table 30***, Dysphagia VAS Swallowing at 24 Months with the PCM group reported a mean score of 8.8 (SD = 16.3) while the ACDF group reported a mean of 12.1 (SD = 20.1). Dysphagia VAS Hoarseness at 24 Months with the PCM group reported a mean score of 7.3 (SD = 14.3) while the ACDF group reported a mean of 10.1 (SD = 18.5).

As reported in ***Table 30***, based on the Bazaz Dysphagia Index, 87.7% (164/187) of the PCM group and 82.6% (123/149) of the ACDF group had Improved or Maintained scores.

vii. Myelopathy Status

Myelopathic status was assessed according to the Nurick's Index, a six-point (0-5) grading scale. A grade 0 indicates no symptoms of myelopathy, and a grade 5 is a bed- or chair-bound patient. As reported in ***Table 30***, 100% (185/185) of the PCM group had Improved or Stable Nurick's assessments compared to 96.7% (148/153) of ACDF patients.

viii. Radiographic Assessments

Radiographic evaluations of motion measurements, angulation and translation (during flexion and extension), at the treated level at the preoperative, 12 Month and 24 Month time points are shown in ***Table 38***.

Table 38: Radiographic Range of Motion for PCM (Per Protocol 24 Months In Window Population)

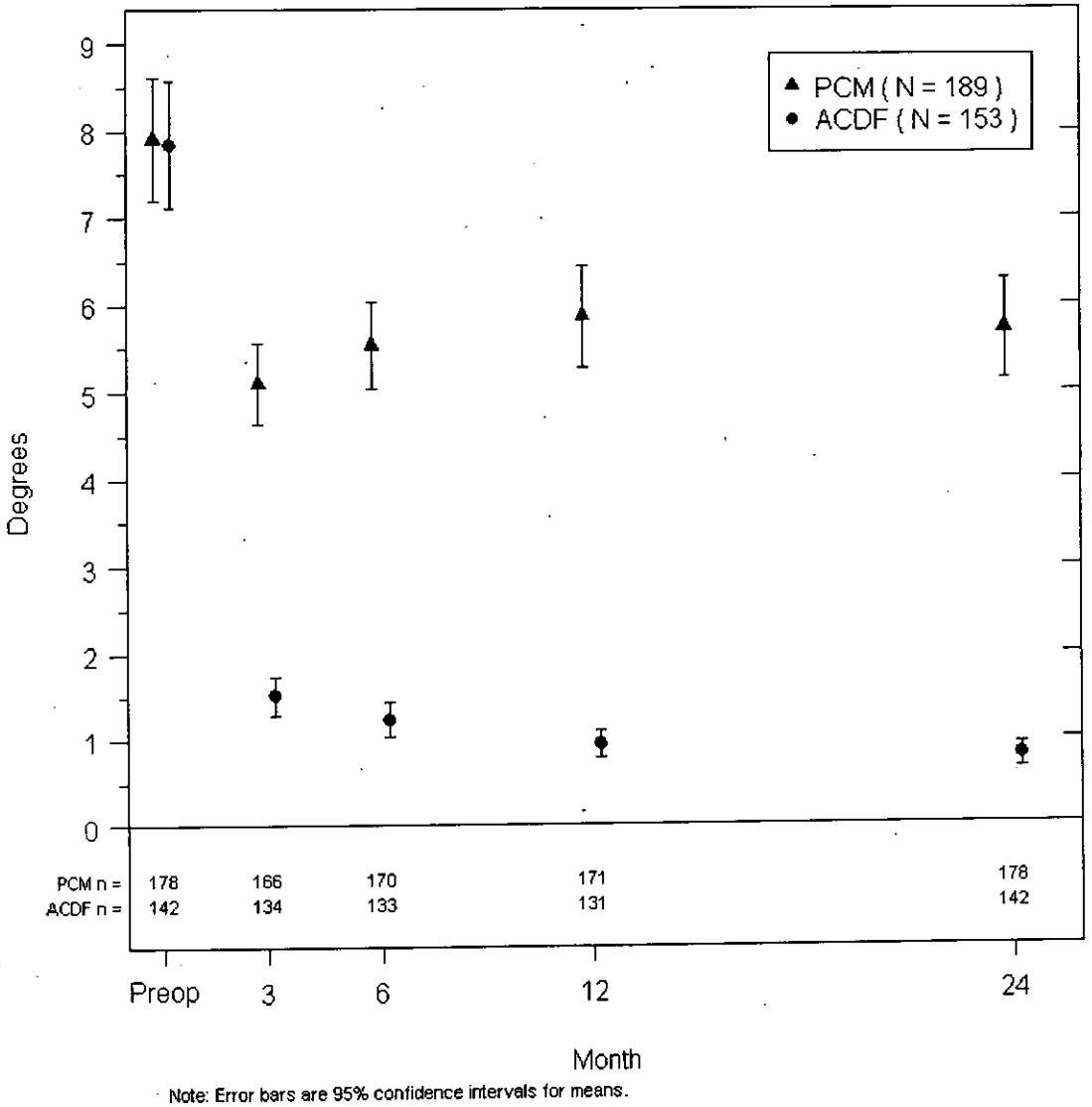
	Preoperative			12 Months			24 Months		
	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)	TRN (N=56)	PCM (N=189)	ACDF (N=153)
n	50	178	142	50	175	138	53	182	151
Range of Motion, mean (SD) degrees	7.9 (4.5)	7.9 (4.7)	7.8 (4.4)	7.2 (4.2)	5.8 (3.9)	0.9 (0.9)	6.6 (4.0)	5.7 (3.9)	0.8 (0.8)
n	49	176	135	48	173	131	51	180	144
Translation, mean (SD) mm	0.8 (0.5)	0.9 (0.6)	0.9 (0.7)	1.3 (1.1)	1.0 (0.7)	0.1 (0.1)	1.2 (1.0)	1.0 (0.8)	0.1 (0.1)

Note: Includes patients who have a valid 24 Month range of motion or translation result.

Range of Motion (ROM):

The average angulation range of motion (flexion-extension arc) for the PCM and ACDF groups at the preoperative, 3 Months, 6 Months, 12 Months and 24 Months visits are illustrated in ***Figure 4***. The mean postoperative ROM for the PCM patients was 5.9° at 12 Months and 5.7° at 24 Months, and the mean ROM for the ACDF patients remained at less than 1°at those time points. With the exception of the preoperative visit, regarding ROM there is a statistical difference between PCM and ACDF at each postoperative visit.

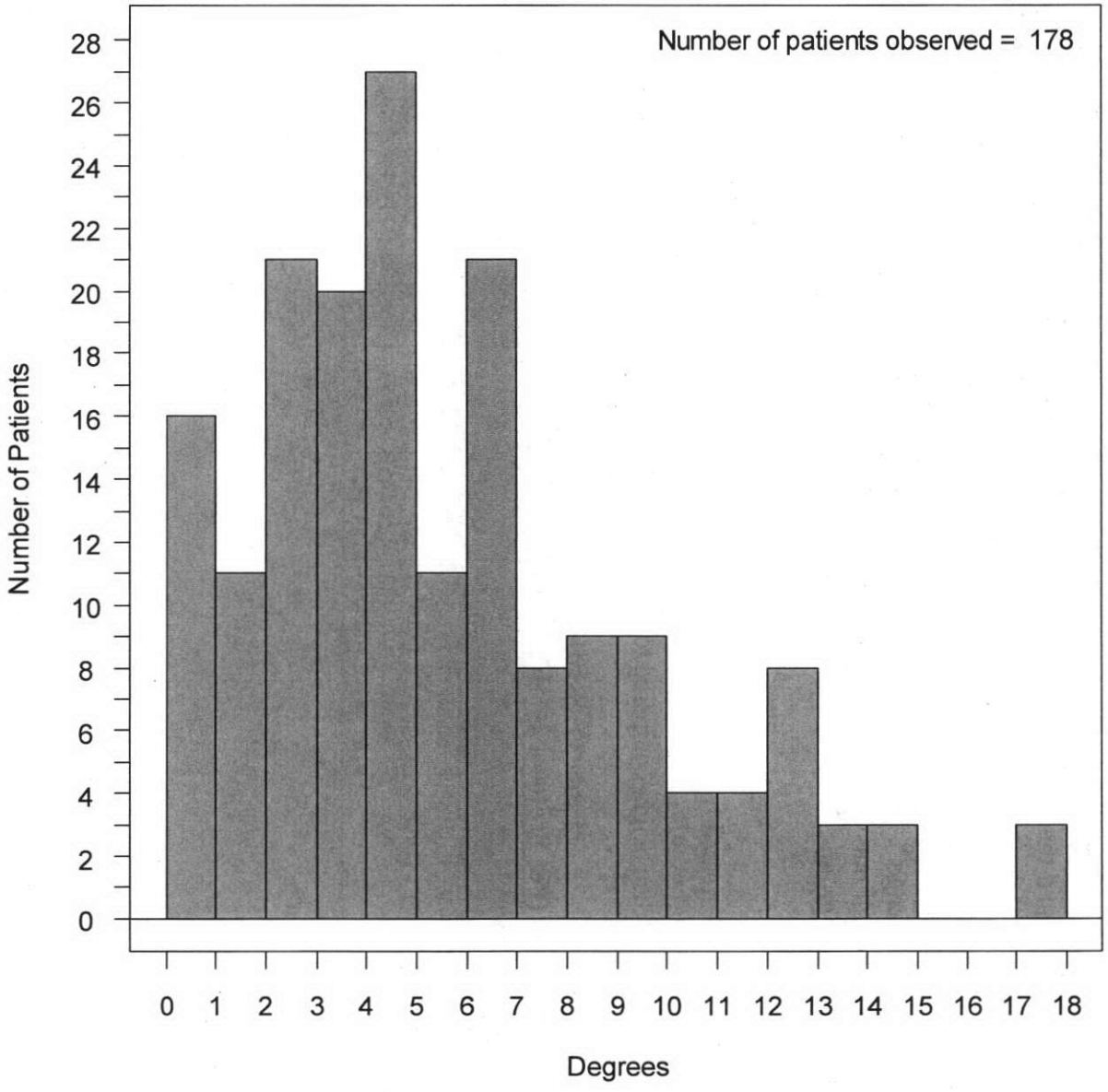
Figure 4: Mean Range of Motion
(Per Protocol 24 Months In Window Population)



Note: Error bars are 95% confidence intervals for means.

A frequency histogram of angular range of motion at 24 Months is provided in ***Figure 5***.

Figure 5: Histogram of Range of Motion at 24 Months for Randomized PCM (Per Protocol 24 Months In Window Population)



Hypermobility:

An additional attempt was made to evaluate whether there was an adjacent level mechanical effect observable on radiograph by using a measurement of hypermobility. Reitman, *et al.*[10] had measured the cervical spine flexion-extension range of motion of a population of normal asymptomatic volunteers. They grouped the ranges of motion by cervical disc level and determined a "normal" range of motion that they defined as the 95% confidence interval of the population.

The adjacent level ranges of motion of patients in the PCM study were then compared to this normative population for matched levels to determine if the observed range of motion was within or above the Reitman "normal" range. By nature of Reitman's definition, 5% of a normal population falls outside the normal range[10]. Thus, to determine that the treated population is different from the normal population, a large percentage of patients would have to fall outside the normal range. As shown in ***Table 30***, the numbers of randomized patients falling out of the normal range was similar between groups.

Disc Height:

Radiographic evaluation of disc height of the treated level at the preoperative, 6 Months, 12 Months, and 24 Months time points are shown in ***Table 39*** for all patients. A disc height equal to 80% or more of the height of the adjacent cephalad disc was regarded as "normal." At 24 Months, 96.7% of PCM patients had normal disc height compared to 85.0% of ACDF patients.

Table 39: Radiographic Disc Height
(Per Protocol 24 Months In Window Population)

	Preoperative			6 Months			12 Months			24 Months		
	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF	TRN	PCM	ACDF
Normal Disc Height (≥80% of Superior Level)	65/65 (100%)	190/193 (98.4%)	151/157 (96.2%)	60/60 (100%)	185/188 (98.4%)	129/151 (85.4%)	58/58 (100%)	178/186 (95.7%)	121/144 (84.0%)	49/51 (96.1%)	176/182 (96.7%)	119/140 (85.0%)
No Change in Disc Height (≥80% of Postoperative)	NA	NA	NA	58/59 (98.3%)	178/182 (97.8%)	121/145 (83.4%)	53/57 (93.0%)	168/180 (93.3%)	114/138 (82.6%)	43/50 (86.0%)	160/177 (90.4%)	112/135 (83.0%)

NA = not applicable.

Radiolucency:

Radiolucency was evaluated at each endplate interface (e.g., superior and inferior, relative to the prosthesis or graft) for both the PCM and ACDF groups. Lucency of greater than 50% of the length of the prosthesis or graft was considered to be significant. Results are provided in ***Table 27***. At 24 Months, 92.3% (168/182) of PCM group and 100% (152/152) of ACDF group's superior interfaces showed no significant lucencies, while at the inferior interface, no significant lucencies were observed in either group; 100% (182/182) of the PCM and 100% (152/152) of ACDF group.

Radiographic Fusion:

Radiographic fusion for ACDF patients was defined by the presence of bridging trabecular bone, no radiolucent lines at ≤50% of the graft-vertebral interfaces, and ≤2° of segmental motion on flexion-extension radiographs. Fusion status of the ACDF group at the 6 Months, 12 Months, and 24 Months time points is provided in ***Table 40***. At the 24 Months, 92.1% (139/151) of the ACDF patients met the radiographic criteria for a successful fusion.

Table 40: Radiographic Fusion Status for Randomized ACDF (Per Protocol 24 Months In Window; N=153)

	6 Months	12 Months	24 Months
Fusion Success*	69/139 (49.6%)	118/138 (85.5%)	139/151 (92.1%)
Range of Motion <2°	109/139 (78.4%)	125/138 (90.6%)	141/151 (93.4%)
Range of Motion <5°	137/139 (98.6%)	137/138 (99.3%)	150/151 (99.3%)

* Fusion success defined by protocol as evidence of continuous bridging bone between the adjacent endplates of the involved motion segment, radiolucent lines at ≤50% of the graft-vertebral interfaces, and ≤2° of segmental movement on lateral flexion/extension x-rays.

Dynamic Canal Stenosis:

Dynamic canal stenosis, as measured on the lateral extension radiograph is a measurement of the width of the spinal canal at the level above the treatment. It has been suggested[10] that a measurement of 12 mm or less on the lateral radiograph represents a significant chance for the spinal cord to be unduly compressed (e.g., stenosed) during an extension motion, which could cause transient or permanent neurological deficiencies.

Each lateral extension radiograph that was available for the 24 Month time point was evaluated radiographically in order to determine if the 12 mm threshold was met. In the PCM group, 99.5% (181/182) and in the ACDF group 97.2% (140/144) of the radiographs so examined demonstrated a canal width of greater than 12 mm, indicating that in the vast majority of cases, dynamic canal stenosis was not present 24 Months following surgery.

Heterotopic Ossification:

Available radiographs for all treated PCM patients at the 6 Months, 12 Months, 24 Months and later time points were assessed by independent radiographic evaluators for heterotopic ossification (HO) grade, based on the modified McAfee scale (Mehren classification system[13]). Results are shown in ***Table 41***. At 24 Months, 95.7% (223/233) PCM patients had Grades 0, Grade I or Grade II HO, and 4.3% (10/233) PCM patients had Grade III or Grade IV HO.

Table 41: Heterotopic Ossification for PCM
(Per Protocol 24 Months In Window Population)

Month	Grade*	Training (N=56)	PCM (N=189)	All PCM (N=245)
6	n (Observed)	49	175	224
	Grade 0	41 (83.7%)	163 (93.1%)	204 (91.1%)
	Grade I	1 (2.0%)	5 (2.9%)	6 (2.7%)
	Grade II	7 (14.3%)	6 (3.4%)	13 (5.8%)
	Grade III	0 (0.0%)	1 (0.6%)	1 (0.4%)
	Grade IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
12	n (Observed)	50	175	225
	Grade 0	30 (60.0%)	132 (75.4%)	162 (72.0%)
	Grade I	7 (14.0%)	26 (14.9%)	33 (14.7%)
	Grade II	13 (26.0%)	14 (8.0%)	27 (12.0%)
	Grade III	0 (0.0%)	2 (1.1%)	2 (0.9%)
	Grade IV	0 (0.0%)	1 (0.6%)	1 (0.4%)
24	n (Observed)	51	182	233
	Grade 0	28 (54.9%)	113 (62.1%)	141 (60.5%)
	Grade I	5 (9.8%)	29 (15.9%)	34 (14.6%)
	Grade II	16 (31.4%)	32 (17.6%)	48 (20.6%)
	Grade III	1 (2.0%)	6 (3.3%)	7 (3.0%)
	Grade IV	1 (2.0%)	2 (1.1%)	3 (1.3%)

* McAfee *et al., Journal of Spinal Disorders*, 2003.[14]

Medication Use and Postoperative Procedures for Pain Management:

Medication use at baseline preoperative and 24 Months postoperative is reported for each group in ***Table 42***. The rate of medication use was similar for all groups at both time points.

Table 42: Medication Use at Baseline and 24 Months Postoperative
(Per Protocol 24 Months In Window Population)

	Training (N=56)	PCM (N=189)	ACDF (N=153)
Baseline			
No Medication Ongoing	15 (26.8%)	51 (27.0%)	38 (24.8%)
No Pain Medication	18 (32.1%)	61 (32.3%)	47 (30.7%)
Any Pain Medication*	38 (67.9%)	128 (67.7%)	106 (69.3%)
Narcotics	27 (48.2%)	93 (49.2%)	87 (56.9%)
Nonnarcotics	18 (32.1%)	62 (32.8%)	42 (27.5%)
Muscle Relaxants	6 (10.7%)	36 (19.0%)	35 (22.9%)
Other	15 (26.8%)	41 (21.7%)	31 (20.3%)
24 Months			
No Medication Ongoing	26 (46.4%)	77 (40.7%)	60 (39.2%)
No Pain Medication	27 (48.2%)	91 (48.1%)	68 (44.4%)
Any Pain Medication*	29 (51.8%)	98 (51.9%)	85 (55.6%)
Narcotics	17 (30.4%)	57 (30.2%)	52 (34.0%)
Nonnarcotics	17 (30.4%)	75 (39.7%)	51 (33.3%)
Muscle Relaxants	7 (12.5%)	29 (15.3%)	31 (20.3%)
Other	8 (14.3%)	36 (19.0%)	27 (17.6%)

* Any Pain Medication is any narcotic or nonnarcotic pain medication usage.

Table 43 shows the cumulative numbers of patients with subsequent secondary surgical interventions at adjacent spinal levels at each time point. A cumulative total of 3.3% of patients in the PCM group had adjacent level surgery compared to 5.8% of patients in the ACDF group.

Table 43: Cumulative Patients with Adjacent Level Surgical Treatment by Time Period (Safety Population)

Period*	Training (N=75)	PCM (N=214)	ACDF (N=190)
6 Weeks	0 (0.0%)	0 (0.0%)	1 (0.5%)
3 Months	0 (0.0%)	0 (0.0%)	1 (0.5%)
6 Months	0 (0.0%)	1 (0.5%)	1 (0.5%)
12 Months	1 (1.3%)	3 (1.4%)	2 (1.1%)
24 Months	3 (4.0%)	5 (2.3%)	6 (3.2%)
36 Months	5 (6.7%)	6 (2.8%)	7 (3.7%)
48 Months†	7 (9.3%)	6 (2.8%)	11 (5.8%)
>48 Months	7 (9.3%)	7 (3.3%)	11 (5.8%)
Total	7 (9.3%)	7 (3.3%)	11 (5.8%)

* Postoperative time period in which surgical treatment occurred.
† Not all patients completed 48 Months follow-up as of September 2011.

The types of surgical interventions that were performed at adjacent spinal levels are provided in *Table 44*. In the PCM group, 3 patients had decompression (laminectomy, laminotomy or foraminotomy) procedures, 2 had a one-level ACDF, and 2 had multi-level ACDF procedures. In the ACDF group, 6 patients had a one-level ACDF, 4 patients had an adjacent level total disc replacement, and 1 had a decompression procedure.

Table 44: Patients with Adjacent Level Surgical Treatment (Safety Population)

Procedure	Training (N=75)	PCM (N=214)	ACDF (N=190)
ACDF at Adjacent Level (1-Level)	2 (2.7%)	2 (0.9%)	6 (3.2%)
ACDF at Adjacent Level (2-Level)	2 (2.7%)	1 (0.5%)	0 (0.0%)
ACDF at Adjacent Level (3-Level)	0 (0.0%)	1 (0.5%)	0 (0.0%)
CTDR at Adjacent Level	1 (1.3%)	0 (0.0%)	4 (2.1%)
Laminectomy, Laminoplasty, Foraminotomy	2 (2.7%)	3 (1.4%)	1 (0.5%)
Total	7 (9.3%)	7 (3.3%)	11 (5.8%)

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The valid scientific evidence presented in the preceding sections provides reasonable assurance that the PCM Cervical Disc is a safe and effective disc replacement for C3-C4 to C6-C7 following single-level discectomy in the treatment of patients with a degenerated cervical disc with accompanying radicular and/or myelopathic symptoms.

A. Safety Conclusions

The risks of the PCM device are based on nonclinical laboratory and animal studies as well as data collected in the clinical study conducted to support PMA approval as described above.

Preclinical testing performed on the device demonstrated that the PCM should withstand the expected physiologic loads in the cervical spine.

In the clinical study, the investigational PCM device was found to have a reasonable assurance of safety and to be at least as safe as the ACDF control treatment. The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The rate of PCM patients having at least one adverse event, an event classified as a surgery-related adverse event, or an event classified by the CEC as a serious adverse event was comparable to the ACDF control group rate. The rate of PCM patients classified as having a device-related adverse event (14% for randomized PCM patients) was numerically lower than the ACDF control group rate (23%). The rate of secondary surgery for PCM (7.5%) was comparable to ACDF group (7.4%). With respect to the subset cohort (PCM-V), the device related adverse events and revision rates were numerically lower than in the PCM Standard cohort; however, subgroup analyses showed that the results were comparable and the cohorts were poolable. The randomized PCM and ACDF control groups demonstrated similar percentages of patients with stable or improved neurologic status at each time point including 24 months (94.7% stable or improved in the PCM group at 24 months as compared to 89.5% stable or improved in the ACDF control group at 24 months).

In conclusion, the clinical study data indicate that, at 24 months postoperatively, the PCM device has a reasonable assurance of safety and is at least as safe as the ACDF control group in regards to adverse event rates, neurologic status, and need for secondary surgery at the index level.

B. Effectiveness Conclusions

In this study, 396 of the 470 Per Protocol patients (84.3%) and 396 of 479 treated patients (82.7%) had 24-month primary endpoint data available for analysis at the completion of the study. Statistical analysis demonstrated that the results from all sites were poolable to determine safety and effectiveness. Patient demographic and baseline data were similar between the treatment groups. Mean surgery time was 15.1 min longer for the randomized PCM group than for the control ACDF group, though the magnitude of the difference is likely not clinically significant.

Overall success was defined in the study protocol as improvement in pain and disability using the Neck Disability Index, no complications or subsequent surgery at the index level, and fusion for the control treatment at 24 months.

Regarding the primary analysis, the PCM group had an overall success rate of 75.1% compared to 64.9% for the ACDF group. The results of overall success, using both the protocol-defined and FDA-defined success criteria, demonstrate that the PCM Cervical Disc is statistically non-inferior to the ACDF group at 24 Months ($p < 0.0001$). Individual components of the primary endpoint of the PCM group were higher than the ACDF group.

To assess the impact of patients with unknown outcomes at 24 months or other potential biases, various sensitivity analyses were also conducted to confirm the robustness of the study conclusions. The results of nearly all sensitivity analyses indicate that the PCM is non-inferior to ACDF at 24 months. The sub-group analyses conducted on the PCM-V cohort determined that the success rates were numerically higher compared to the PCM-Standard group; however, the results were comparable and the cohorts were poolable.

Most secondary measures of effectiveness were comparable between groups at 24 Months, such as NDI, neck and arm pain VAS, SF-36, and Bazaz for dysphagia. Therefore, it can be concluded that the PCM Cervical Disc is at least as effective of a treatment as ACDF for the indications studied.

In conclusion, the study data indicate that, at 24 months postoperatively, the PCM device is at least as effective as the ACDF control group in terms of clinically significant improvement on the Neck Disability Index, maintenance or improvement in neurological status, subsequent surgeries at the index level, device-related adverse event rates, and overall success according to both composite definitions analyzed.

C. Benefit-Risk Conclusions

The probable benefits of the PCM device are also based on data collected in the clinical study conducted to support PMA approval as described above.

The clinical study demonstrated several benefits of the PCM device over the 24 month time period studied.

- The benefit of the PCM in terms of clinically meaningful improvement in function (as measured by a 15-point improvement on the Neck Disability Index) at 24 months postoperatively was comparable to the standard of care, ACDF, in that the majority of patients in both treatment groups in the clinical study experienced this benefit (79.7% of randomized PCM patients and 75.5% of ACDF patients).

- The benefit of the PCM in terms of maintenance or improvement in neurologic status (as measured during the neurological examination done by the investigator) at 24 months postoperatively was also comparable to the standard of care, ACDF, in that the majority of patients in both treatment groups in the clinical study experienced this benefit (94.7% of randomized PCM patients and 89.5% of ACDF patients).

- In terms of improvement in neck and arm pain (as measured by either a 20mm improvement in pain on a Visual Analog Scale as compared to baseline or 0mm of pain at the visit), at 24 months postoperatively, the benefit of the PCM was at least comparable to the standard of care, ACDF. Again, the majority of patients in both treatment groups in the clinical study experienced the benefit of improvement in neck and/or worst arm pain (74.3% of randomized PCM patients and 75.3% of ACDF patients with clinically meaningful neck pain improvement at 24 months and 79.1% of randomized PCM patients and 75.3% of ACDF patients with clinically meaningful worst arm pain improvement at 24 months;).

In addition, although the sponsor did not formally collect data on patient tolerance for risk and patient perception on benefit, the patients' perception of their benefit and risk was indirectly measured through a Patient Satisfaction Index (Odom's Criteria). At 24 months, the majority of PCM patients perceived to have an excellent result (68.6% of randomized PCM patients) as compared to a numerically lower excellent result rate in the ACDF control group (53.6% of ACDF patients).

The rate of secondary surgical interventions at the index level in the PCM patients (9.3% [7] of the non-randomized training PCM patients and 5.1% [11] of the randomized PCM patients), was comparable to the ACDF group (5.4% [11] of ACDF patients with an index level secondary surgery) at 24 months. Including longer term follow-up (>24 Months), the rate of secondary surgical intervention at the index level was again comparable between the PCM patients (12.0% [9] of the non-randomized training PCM patients and 7.5% [16] or randomized PCM patients) and the ACDF patients (7.4% [14]).

Several additional factors were considered in determining the probable benefits and risks for the PCM device. Limitations of the clinical study design, including the inability to mask patients to their treatment assignment, reliance on subjective endpoints, concerns about potential placebo effect, and subjectivity in adverse event classification, were considered. In addition, the impact of missing data and the robustness of the sensitivity analyses provided to address the missing data as well as the generalizability of the study results were also considered. Finally, alternative available treatments and risk mitigation strategies were considered as was the fact that the only available indicator of patient tolerance for risk and perspective on benefit was patient satisfaction data.

Note that other theoretical benefits of total disc replacement devices, such as the PCM, include preservation of range of motion and decreased risk of adjacent segment degeneration; however, the clinical study conducted to support PMA approval of the PCM was not specifically designed or powered to study these potential benefits as primary endpoints, and any potential benefit in terms of clinically significant reduction in adjacent level degeneration would not necessarily be expected in the two year time period of the clinical study.

In conclusion, given the available information above, the data support that for reconstruction of the disc at one level from C3-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space and specific radiographic findings as outlined above in the Indications for Use, the probable benefits of the PCM outweigh the probable risks through two years follow-up.

D. Overall Conclusions

The preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of the PCM Cervical Disc when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that the clinical benefits of the use of the PCM Cervical Disc in terms of improvement in pain and disability, and the potential for motion preservation, outweigh the risks associated with the device and surgical procedure through two years follow-up when used in the indicated population in accordance with the directions for use.

XII: PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopaedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH issued an approval order on October 26, 2012. The final conditions of approval cited in the approval order are described below.

The Sponsor has agreed to provide the following data as part of the annual report:

1. A literature review each year for related published data on the PCM and similar products to identify and summarize clinical advantages, disadvantages, cautions, warnings and adverse events.

2. The applicant must attempt to retrieve all explanted PCM devices (including but not limited to those retrieved from patients in the PAS and ESS). All retrievals will be analyzed and reported per the agreed Explant Analysis protocol.

In addition to the Annual Report requirements, the applicant must provide the following data in post-approval study reports (PAS). Two (2) copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. *Extended Follow-up of Premarket Cohort*: The applicant must perform a 7-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the PCM Cervical Disc as compared to anterior cervical discectomy and fusion (ACDF) by following the 357 patients from the pivotal investigational device exemption (IDE) study (222 PCM patients, and 135 ACDF patients) annually through 7 years. At each annual (±6 month) visit, you will collect the following data: Neck Disability Index (NDI), neck and right/left arm pain Visual Analog Scale (VAS), health status survey (SF-36), patient satisfaction, neurological status, radiographic information, work status, and all adverse events regardless of cause. Radiographic information collected will include: range of motion on flexion/extension films (angulation and translation as well as the correlation of range of motion with outcomes), disc height, radiolucency, device displacement or migration, spinal fusion (control group only), and heterotopic ossification You will also report data on adjacent level degeneration

   The primary objective of the study is to evaluate the overall success rate, using Overall Success Definition 1, defined as:

   - Pain/Disability Improvement of at least 20% in the Neck Disability Index (NDI) at 7 years compared with the score at baseline;
   - No device failures (at the index level) requiring revision, re-operation, removal, or supplemental fixation;
   - Absence of major complications defined as major vessel injury, neurological damage, or nerve injury;
   - Maintenance or improvement in all components of neurologic status; and
   - Radiographic success (For PCM patients, defined as lack of evidence of continuous bridging bone between the adjacent endplates of the involved motion segment or >2° of segmental movement on lateral flexion/extension radiographs. For ACDF patients defined as evidence of continuous bridging bone between the adjacent endplates of the involved motion segment, radiolucent lines at ≤50% of the graft-vertebral interfaces, and ≤2° of segmental movement on lateral flexion/extension radiographs).

   The applicant conduct an additional analysis evaluating Overall Success Definition 2, defined as follows:

- Pain/Disability Improvement of at least 15-points in the Neck Disability Index (NDI) at 7 years compared with the score at baseline;
- No device failures (at the index level) requiring revision, re-operation, removal, or supplemental fixation;
- Absence of major complications defined as major vessel injury, neurological damage, or nerve injury;
- Maintenance or improvement in all components of neurologic status; and
- Radiographic success (For PCM patients, defined as lack of evidence of continuous bridging bone between the adjacent endplates of the involved motion segment or >2° of segmental movement on lateral flexion/extension radiographs. For ACDF patients defined as evidence of continuous bridging bone between the adjacent endplates of the involved motion segment, radiolucent lines at ≤50% of the graft-vertebral interfaces, and ≤2° of segmental movement on lateral flexion/extension radiographs).

Success rates between the randomized Per Protocol investigational and control groups will be compared and assessed for non-inferiority based on 10% non-inferiority margin for both overall success definitions. Patients who were non-recoverable non-responders prior to 24 months will carry forward as failures for each subsequent annual visit. Several sensitivity analyses will also be done.

FDA will expect at least 85% follow-up at the 7-year time point to provide sufficient data to evaluate safety and effectiveness.

2. *Enhanced Surveillance System*: The applicant must perform a 10-year Enhanced Surveillance Study (ESS) of the PCM Cervical Disc to fully characterize serious device-related adverse events when the device is used in the intended patient population under general conditions of use in the United States and in the rest of the world. The applicant will passively collect, analyze, and submit all serious device-related adverse event data including subsequent surgeries, heterotopic ossification, and other device issues. This information will be collected through complaints and MDRs, explant analysis, and literature review.

   In addition, the applicant will actively collect surgeon feedback annually to elicit information related to heterotopic ossification, device malfunction, device removal, or other serious device-related complications. This information will be collected using surgeon surveys. All of the surgeons who have been trained on the use of PCM in the U.S. will be surveyed annually and the number of surveys issued and received will be reported. If a survey response includes any information related to an adverse event, you will collect additional data as specifically outlined in the ESS protocol and report that data to FDA.

   The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling.

Post Approval Requirements and Restrictions: See the Approval Order.

XV. REFERENCES

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